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OPUSCULA NEUROLOGICA

KNUD H. KRABBE

DIE III. MARTII

ANNO DOMINI MCMLV

DEDICATA

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KNUD H. KRABBE

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1939 Vore nerver og krigen.
1940 Årsag og virkning i lægekunsten.
1940 Isseøje og koglekirtel. Et gådefuldt organs historie.
1941 Overtro og tvangstanker.
1942 Kæmper og dværge.
1943 Et svensk forskningsinstitut for studiet af fosterudviklingen.

EDITORSHIP AND CONTRIBUTORSHIP

- From 8/2-1906 to 9/6-1906 editor of the *Akademisk Foreningsblad*.
From 1/1-1926 editor of the *Acta psychiatrica et neurologica Scand.*
From 1915 to 1930 contributor to *Salmonsens konversationsleksikon*, 2. udg.
From 1937 to 1940 contributor to the *Lille Salmonsens*.
From 1941 contributor to the *Salmonsens Leksikon-tidsskrift*.
From 1941 contributor to the *Rassegna Internazionale de Clinica e Terapia*.
From 1941 contributor to the *Endocrinology*.
From 1941 contributor to the *Confinia Neurologica*.
From 1946 contributor to the *Excerpta Medica*.
From 1950 member of the Advisory Board of the *Journal of Neuropathology and Experimental Neurology*.
From 1946 to 1950 contributor and editor of articles on medicine in *Den nye Salmonsens*.

MEMBERSHIP AND HONOURS

- 1922 Corresponding, later honorary member of the *Société de Neurologie de Paris*.
1924 Corresponding member of the *Philadelphia Neurological Society*.
1938 Corresponding member of the *Societas Neurologiae Estoniensis*.
1939 Corresponding member of the *Société d'Endocrinologie*.
1945 Associated member of the *Nordisk neurokirurgisk forening*.
1946 Corresponding member of the *Svensk Neurologisk Förening*.
1948 Honorary member of the *New York Neurological Society*.
1948 Honorary member of the *American Neurological Association*.
1949 Corresponding member of the *Société Suisse de Neurologie*.
1949 Honorary member of the *Sociedad Española de Neurología*.
1949 Honorary president of the *Reunion Inaugural de la Sociedad Española de Neurología*.
1949 Vicepresident of the *IV International Neurological Congress (Paris)*, president of the *Electroencephalographic Section*.
1950 Honorary doctor of the *Medical Faculty at the University of Lund, Sweden*.
1950 Honorary member of the *American Academy of Neurology*.

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- 51 Honorary doctor of the Kungl. Karolinska Medico-kirurgiska Institutet, Sweden.
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- 52 Appointed to the International Panel of Corresponding Neurologists. National Multiple Sclerosis Society.
- 53 Vicepresident of the V International Neurological Congress in Lisboa.
- 54 Honorary member of the Nederlandsche Vereeniging voor Psychiatrie en Neurologie.
- 3-1949 An honorary grant from the Martin Salomonsens Foundation in recognition of his studies on the development of the brain.
- 9-1949 Chevalier de la Légion d'Honneur (France).
- 9-1950 An honorary grant from the Foundation of the Otologist Valdemar Klein and the Physician, Mrs. Klein.

REVISED QUECKENSTEDT TEST

(With special reference to the diagnosis of cervical
disc protrusions)

By

ERIK DA CUNHA BANG

In later years spondylosis of the cervical spine has been an object of great interest to neurologists, as the accompanying osteophytes and disc protrusions by pressure on the spinal cord and/or nerve roots may produce clinical pictures closely resembling: disseminated sclerosis, amyotrophic lateral sclerosis, syringomyelia, subacute combined degeneration, other conditions causing progressive spastic paraplegia, spinal tumour and radiculitis (*Brain et al.*). The disease is of so great interest as, in contrast to most of the disorders mentioned, it can often be treated effectively, either surgically or conservatively with supporting collars. The diagnosis is made with increasing frequency partly owing to improvements in the x-ray technique with introduction of oblique views, functional examination, tomography and the most important: myelography. This examination should be made in uncharacteristic cases of the above-mentioned disorders, where the neurological signs do not reach rostrally of the cervical cord, as well as in cases of suspected tumour. However, in this country we are still rather reticent with regard to the use of myelography, partly because Panto-paque is not considered absolutely harmless (*Christensen & Hertz*), and partly because cervical air myelography is not yet widely in use.

The object of the present paper was to investigate whether another important auxiliary in neurological diagnosis, lumbar puncture, could be improved so as to give information helping to differentiate between the disorders mentioned and thereby clarifying the indication for myelography.

When introducing his test in 1916 *Queckenstedt* said that this could not be used to differentiate between block caused by intrinsic

and extrinsic cord processes. The technique of the test has not changed much since then, until *Kaplan & Kennedy* in 1950 described their modification of compression of the jugular veins in different head postures, a kind of functional investigation, where the test was carried out with the head first in a "neutral" position, then fully flexed and finally fully extended. Later on they added further modifications with lateral flexion and rotation. The test was carried out with the patient in the lateral supine position as usual, with no more than 90° of flexion of the thighs in order to avoid abdominal compression. After each jugular compression abdominal compression was done to assure free connexion. Using this technique 341 lumbar punctures were applied to 294 patients. In order to secure the specificity of the test the investigation included a wide variety of neurological disorders without suspicion of cord compression, 253 patients in all, and all these had normal manometries. 6 patients had partial or complete manometric block unrelated to head postures on account of cord tumours in the thoracic or lumbar region. The object of the investigation was primarily to try to explain the absence of any manometric block in a number of surgically confirmed compressing lesions, and secondarily to explain the presence of what appeared to be a complete manometric block in cases with normal spinal fluid protein contents (cf. *Wagner*).

31 patients had clinically diagnosed compression of the cervical cord. 3 of these showed complete subarachnoid block unchanged by variation of head posture (character of lesion not mentioned). 16 patients showed no block, but nevertheless 7 of these were operated on: 6 had no demonstrable lesion and 1 had a slight filmy arachnoiditis. The remaining 12 had either complete or partial block in one or more head postures; of these 9 in extension solely (7 complete, 2 partial), 1 complete in extension and partial in the other postures, 1 complete in flexion solely, and 1 complete in atypical position. Out of the 10 who showed isolated or predominant block in extension, 8 were operated on: compressing exostoses of the cervical spine (arthritic or calcified disc protrusions) were found in 4 cases, herniated discs in 2 cases, and arachnoiditis in 2 cases. Pantopaque-myelograms were performed in 4 cases before surgical intervention, and hereby the abnormality revealed by the Queckenstedt test could be visualized: with the head in the hyperextended position there was complete stoppage of the Pantopaque above the level of the lesion, and then as the head was slowly flexed, the Pantopaque began to trickle down, outlining the protrusion. 1 of the 4 who were not operated on recovered spontaneously, the others are not mentioned specifically (in particular not the patient with block solely in flexion), except for the fact that none of the 12 had tumours.

of the patients had elevated spinal fluid protein contents. In 5 cases the test was repeated after decompressive laminectomy and normal results were ascertained.

Thus the test showed block in cases in which the usual technique could have failed to reveal any abnormality. In the presence of intermittent block related to head posture a satisfactory explanation to the above-mentioned questions was found. No explanation of the phenomenon was given, except that it was supposed that a mechanical factor might have played a part, as 5 of the 8 operatively demonstrated lesions were localized to the C 5/6 level, which as a rule is the pivotal point for movement of the cervical spine.

However, several other authors without having made manometric studies have pointed out that hyperextension of the spine causes the intervertebral discs to protrude backwards, slightly in normal cases and rather more in cases of disc protrusions. By means of myelography *Lumberlain & Young* have shown, that this applies to lumbar discs, and in their excellent article on cervical spondylosis *Brain et al.* mention that in most cases extension of the cervical spine causes most distortion of the cord; this they also demonstrate by myelography. In cases of cord compression caused by cervical disc protrusions *Mair & Druckmann* found on autopsy that the protrusion in flexion was only slight, but more pronounced in extension.

These findings explain the majority of *Kaplan & Kennedy's* positive results, and it is tempting to suppose that this phenomenon is a special characteristic of disc protrusions and therefore of value in diagnosis. However, it has been shown that arachnoiditis can produce similar intermittent block related to head posture, and other investigators, even in pronounced cases of cervical spondylosis with compression of the cord, have been unable to demonstrate any significant influence of flexion and extension of the head on the manometric findings (*Spillane & Lloyd: 21 cases with only one partial block*).

In an attempt to elucidate these matters and by the use of *Kaplan & Kennedy's* technique I have examined 77 patients (79 lumbar punctures). 66 patients showed normal records and 11 patients showed some kind of block. Normal records were found in 33 males and 33 females between the ages of 19-76 (Table I).

Kaplan & Kennedy maintained that 2 observers ought to be present, one for the sole purpose of managing the changes in head posture and compression of jugular veins, but in the present investigation one was found to be sufficient. No attempt was made to record the absolute basic pressure in the different head postures, as a reliable recording would prolong the test unnecessarily (*Solemon et al.; Lunn*).

TABLE I

Cephalalgia, psychoneurosis	13
Spondylosis cervicalis	19
Encephalitis, sclerosis disseminata	8
Lues cerebrospinalis	4
Neuritis, radiculitis	10
Prolapsus disci lumbalis	6
Sclerosis amyotrophica lateralis	2
Syringomyelia	4
	66

but only the variations in pressure have been compared. The jugular compression was carried out for 10 seconds, the pressure then being recorded every 10 seconds, until the original level was reached, or nearly. In normal cases the rise and decline of pressure may of course be completed in less than 10 seconds (*Fog & Ravn*), but in cases of partial block it will always take longer, rendering more frequent recordings unnecessary (*Fig. 1*).

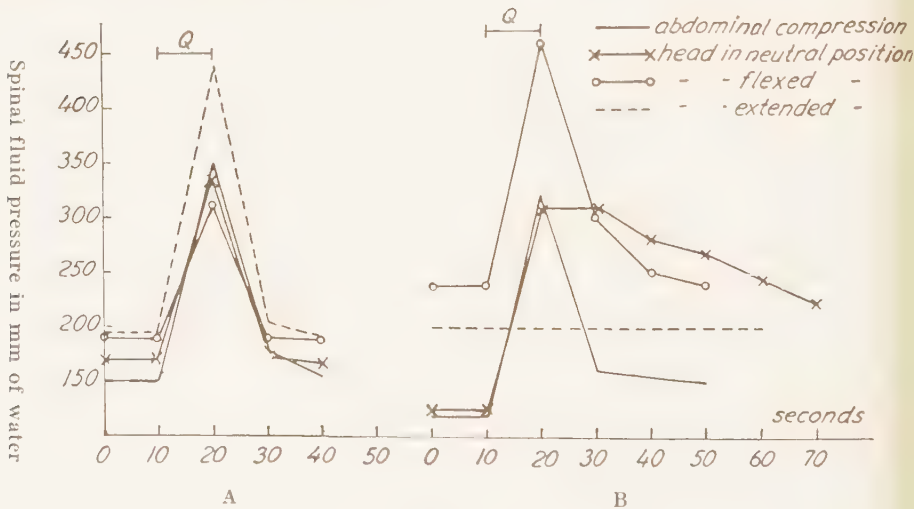


Fig. 1.

A: Normal record.

B: Normal record in flexion,
partial block in the neutral position,
complete block in the extended position.

The commonest finding was that the greatest rise and decline occurred when the head was held extended (two thirds of the cases). The variations in pressure were in three cases only less in extension

man in the other positions, but in no case so slight as to give a suspicion of block. The freer rise and decline in extension in most cases might possibly support the theory that the capacity of the subarachnoid space is greatest in this position, a fact used in explaining the characteristic posture of meningitis, but it might just as well be the result of the compression being undertaken most easily in this position.

It is very important that the position of the needle is continually controlled by abdominal compression. A block was found in one case, but as displacement of the needle was suspected, repuncture was made and normal conditions revealed.

It is just as important to carry out the extension in full. Patients suffering from cervical spondylosis often try to resist extension, as this sometimes produces unpleasant paraesthesiae down the back and down the legs. In another hospital a case of intermittent block was overlooked, which on repuncture and more thorough extension could be clearly demonstrated (naturally with due regard to the risk of cord compression).

Experiments with the head rotated did not on any occasion give any supplementary information of value.

In 11 cases abnormal manometrics were revealed: 2 had a total block resulting from space-occupying lesions in the thoracic part (fracture, metastasis), which of course was unrelated to the head posture; and one, who had a high cervical intramedullary tumour, had a partial block in the neutral and in the flexed position, but normal passage in the extended position. However, this finding was of no great value, as four years ago the patient had been treated surgically with a decompressive laminectomy, because the tumour could not be removed.

The remaining 8 patients, who all suffered from cervical spondylosis, and who all had a block, varying with head postures, are summarized in Table II.

The distribution of age and sex corresponds to the ordinary statistics: the majority in the 6th decade and the majority being males. Only 2 of the patients had sustained adequate injuries previously (JH and KL, 5 and 30 years ago, respectively). In the remaining cases the symptoms had appeared gradually. It is a notable fact that all of them had a block in extension, either complete or partial, and 2 of them also had a block in the neutral position, but none of them in flexion. This means that ordinary technique would have failed to reveal a block in at least 6 cases out of 8. In one case only the diagnosis of disc protrusion was not verified - this patient was only slightly in-

TABLE II

Pt	Age	Sex	Duration of illness	Signs		Roentgenograms		Queckenstedt			CSF protein	Level of disc protrusions		
				cord-	root-	nar. discs	post. osteof.	neur.	flex.	ext.		myelography	operation	autopsy
RJ	48	m.	1 yr.	+	+	+	+	NB	NB	PB	25 mg%	no abn.	6/7-7/Th.1	
FH	33	m.	1 yr.	+	+	+	—	CB	NB	CB	34 mg%	4/5	4/5	
AS	39	f.	8 mos.	+	(+)	—	—	NB	NB	PB	400 mg%	5/6	5/6	
KL	59	m.	9 yrs. (30 ")	+	+	+	+	NB	NB	CB	180 mg%	3/4	3/4	
PB	54	m.	?	(+)	(+)	—	—	PB	NB	CB	135 mg%	4/5-5/6		
ND	63	m.	10 mos.	—	+	+	+	NB	NB	PB	110 mg%	4/5-5/6	no abn.	4/5-5/6
CJ	54	f.	6 yrs.	+	+	+	+	NB	NB	CB	145 mg%	5/6	5/6-6/7	
HN	56	m.	4 mos.	(+)	(+)	+	+	NB	NB	CB	36 mg%	not done		

NB: no block. PB: partial block. CB: complete block.

The raised protein values are approximate, being measured according to the method of Neel and worked out in mg% by multiplication with the factor 4.5 (*Brooger*).

capacitated by the ailment in question, but the more so by concomitant disorders, for which reason he refused myelography. The diagnosis was made from plain x-rays.

The remaining 7 were all submitted to myelography and 6 of these were surgically treated. Hard protrusions were discovered in 5 cases and as only a little could be removed, decompressive laminectomy had to be resorted to. In the case of the 6th patient, who only had root symptoms, myelography had revealed protrusion of the discs C 4/5 and 5/6, but this finding could not be confirmed on operation, which took place with the patient sitting in a chair with the head extremely flexed. 13 days after the operation the patient died of embolism of the pulmonary artery. On autopsy it was shown, in accordance with the previously mentioned investigations, that the protrusions of the cervical discs 4/5 and 5/6 were only slight in flexion, but considerably increasing during extension and with an extra knob-formed protuberance opposite to the affected root.

The last patient (PB) was admitted to the hospital with symptoms of acutely ruptured lumbar disc, which during three weeks had caused severe paresis and disturbances of sphincter functions. However, there were also mild signs of cord damage, including a classical inversion of the radial reflex on both sides. Pantopaque myelography (Fig. 2) revealed a complete block at the level of C 4/5 and 5/6, when the head was extended, but free passage in flexion. Opposite the 3rd lumbar disc there was another stoppage. The lumbar lesion being the most important, this was only dealt with surgically, and after the removal of a large free prolapse from the 3rd lumbar disc the patient recovered rapidly. The cord signs also disappeared (immobilisation in bed, and possibly the accompanying slight flexion of the head might have played a part), and only the inversion of the radial reflex remained, suggesting a lesion of the cervical cord. The patient was therefore discharged for further control.

This series seems to support the theory that the revised Queckenstedt test is of special value in demonstrating cervical disc protrusions. It is remarkable that under these conditions block is especially inclined to appear when the head is extended, i.e. in the position where the subarachnoid space is presumed to have its greatest capacity. This might be of value in distinguishing protrusions from other space-occupying lesions, as one would expect that the latter would show the earliest block in flexion. Unfortunately, on account of the rarity of cervical tumours, it has only been possible to investigate the conditions in one case, and although the findings here might support the hypothesis suggested, its significance was compromised by a previous laminectomy.

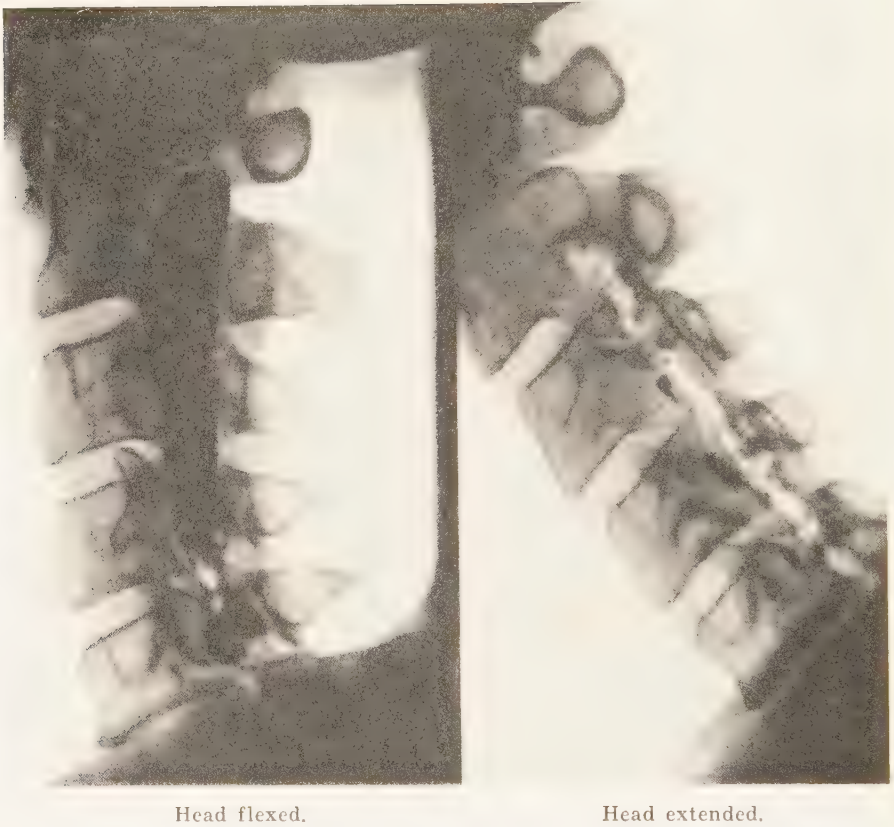


Fig. 2.

It is not, therefore, possible to maintain that the appearance of block in extension is significant for cervical disc protrusions. Besides, others have noticed the same phenomenon in arachnoiditis. Neither can the test be used to exclude the possibility of cervical disc protrusion as the cause of spinal cord signs, as these may appear before the protrusion is sufficiently large to block. The mechanism of this is not clearly understood; it is supposed that interference with the vascular supply (*Brain et al.*) or traction on the dentate ligaments (*Bedford et al.*) may play a part. Such cases are not included in this series, but this may be a mere coincidence.

The conclusion is that the revised Queckenstedt test is of value in the early discovery of space-occupying cervical lesions, which cannot be demonstrated by any ordinary technique. It represents an important factor in distinguishing space-occupying lesions from the other disorders of the cervical cord previously mentioned, but one must continually bear in mind that only the positive result of the test is of

significance. The appearance of block always indicates myelography, especially as, in cases of cervical disc protrusions, an exact diagnosis of the level of the lesion cannot be made on clinical grounds, since the protrusions are often multiple. When using myelography the same functional examinations as with lumbar puncture should be carried out, as otherwise there is a risk of overlooking a protrusion.

SUMMARY

A revised form of Queckenstedt's test introduced by *Kaplan & Kennedy* is described, in which jugular compression is carried out in different head postures: neutral position, full flexion, and full extension. The test is suitable for the early demonstration of cervical space-occupying lesions, as it can reveal blocks which ordinary technique would fail to demonstrate. A block found by this test is always pathological and indicates myelography. 8 patients with cervical spondylosis causing cord compression and 1 patient with an intramedullary tumour of the cervical cord are discussed in detail. The test seems to be of special value in cases of cervical disc protrusions, as these discs have a tendency to protrude when the head is extended and to diminish, when the head is flexed, thereby producing a block in extension, but not in flexion. As cervical spondylosis may produce clinical pictures closely resembling disseminated sclerosis, amyotrophic lateral sclerosis, and other disorders of the cervical cord, this test may be of great help in differential diagnosis, although it is only the positive result that is of significance. It is uncertain whether the appearance of intermittent block can be used to differentiate between protrusions of discs and cervical tumours; but it might be expected that protrusions might be especially liable to produce a block in extension and tumours in flexion. The same technique is recommended for myelography, and it is stressed that a negative exploratory laminectomy does not exclude the presence of a disc protrusion, if the patient is operated on with the head in full flexion.

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QUELQUES RÉFLEXIONS A PROPOS D'UN SYNDROME RUBRO-SUBTHALAMIQUE DE NATURE ENCEPHALITIQUE

Par

LUIS BARRAQUER-FERRÉ et LUIS BARRAQUER-BORDAS

Des syndromes topographiques et des processus morbides connus par les neurologues depuis longtemps, nous soumettent encore aujourd'hui d'ardus problèmes d'interprétation physiopathologique, pathogénique, nosographique, etc. De cette manière ils nous éclairent sur la continuité ininterrompue des efforts que doit déployer la neurologie clinique pour connaître encore plus et mieux les questions correspondant à son champ d'étude.

Nous voulons rendre hommage en son 70^e anniversaire au Prof. Knud H. Krabbe, cet éminent neurologue en qui nous avons toujours trouvé autant un chevalier exemplaire qu'un cordial ami, en relatant une petite observation clinique qui, si elle s'encadre bien dans des profils syndromiques et étiologiques bien connus depuis une trentaine d'années, ne laisse pourtant pas de susciter d'intéressants problèmes d'interprétation en relation avec nos connaissances modernes.

Jacinto Ll., un jeune homme de 19 ans, se présente pour la première fois à la consultation externe de la Clinique de Neurologie de l'Hôpital de la St^a. Cruz y San Pablo, le 12 Mars 1954. Il est garçon de café.

HISTOIRE DE SA MALADIE ACTUELLE

Vers la mi-janvier il commença à souffrir de ce que nous pouvons lénommer un *blépharospasme* gauche dont les contractions se produisaient, au début, de temps en temps. et par la suite beaucoup plus fréquemment. Il présenta aussi, semble-t-il, quelques *clonies faciales*, mais un petit peu, d'une autre topographie.

Un mois plus tard apparut le *hoquet*, qui persista non modifié pen-

dant plusieurs jours, jour et nuit. Il en souffre encore maintenant de temps en temps.

Presqu'en même temps qu'apparaissait le hoquet, il s'établit en une huitaine de jours un syndrome composé par une *hémiparesthésie et hémihypoesthésie gauches*, accompagnées de *dystonie et manque d'assurance dans la main du même côté*.

Ces troubles persistent encore malgré qu'ils se soient lentement améliorés.

La *fièvre* se présenta pendant les jours où le dit syndrome était le plus florissant mais on ne peut la préciser car le thermomètre ne fut pas mis.

Il souffrit aussi de légères insomnies, se reveillant fréquemment. Jamais d'hypersomnie.

Certains jours, une légère céphalée. « Tête incertaine » avec tendance au vertige pendant les premiers jours, sans qu'il réfère un vertige vestibulaire typique. Constipation discrète.

Il n'accuse pas de douleurs, dyplopie, polyurie, polydipsie.

EXPLORATION NEUROLOGIQUE

Ce qui attire tout de suite l'attention en observant le patient, c'est la *dystonie de la main gauche* et les *mouvements discrets du type athétosique* quelle présente.

Les photographies adjointes démontrent l'aspect de cette main typiquement thalamique ou subthalamique.

Quand le patient fait quelque mouvement, ou simplement en marchant, les doigts de la main gauche ont de petits déplacements légers et lents du type athétosique.

Également du côté gauche, on constate des zones, de distribution irrégulière d'*hypoesthésie superficielle*, plus accentuées pour les *sensibilités thermiques* que pour la douleur ou le tact. Cette hypoesthésie est plus importante au niveau de la racine d'un membre inférieur et de la fosse iliaque.

Il n'existe pas d'hyperpathie.

Dans la main gauche on constate une *stéréoanesthésie absolue* et des *défauts de l'arthro cinétique*.

Dans le pied, légers troubles de l'arthrocinétique.

La *sensibilité vibratoire* est *inexistante* dans tout le côté gauche.

Il existe une sensation de constriction dans l'hémithorax gauche.

Dans l'épreuve « doigt-nez » on a gauche on constate *léger tremblement* qui n'augmente pas sensiblement en fermant les yeux.

Légères oscillations à gauche dans l'épreuve « talon-genou ».

Discrète incoordination à gauche dans l'épreuve des marionnettes.

On ne constate pas d'asynergie dans aucune des épreuves classiques de Babinski.

Légère augmentation de la passivité dans les extrémités gauches.

Dans la marche à yeux fermés, on remarque parfois de légères pulsions latérales, généralement vers la gauche, de petite intensité.

Le signe de Romberg est négatif.

Il n'existe d'aucun côté un déficit pyramidal appréciable.

Les réflexes musculaires profonds des deux extrémités inférieures sont modérément vifs.

Ceux des extrémités supérieures sont imperceptibles, même inapparents à gauche, tandis qu'à droite on apprécie seulement avec certitude un bicipital très faible.

Les réflexes cutanés plantaires sont indifférents des deux côtés.

Les cutanés abdominaux sont faibles à droite et inapparents à gauche.

Il n'y a pas de réflexes de défense.

L'extensibilité est un peu supérieure à gauche, le malade étant droitier.

Il n'existe pas de syncinésies de coordination.

Dans l'extrémité supérieure gauche, on constate une faible syncinésie d'imitation.

On peut considérer comme bonnes les réactions d'attitude dans la manœuvre de la poussée.

Légère froideur de la main gauche.

Il n'y a pas de troubles des sphincters.

Motilité oculaire correcte.

Pas de nystagmus.

Le reste de l'exploration neuro-ophtalmologique (fundus, champs visuels, etc.), réalisée en partie avec la collaboration de l'Institut Barraquer d'Ophtalmologie, est aussi normal.

On soigne particulièrement l'investigation du champ visuel, qui fut menée à bout avec la lumière blanche, bleue, rouge et verte.

L'indice était un objet de 5 mm. de diamètre situé à 330 mm. de distance.

Le résultat fut, nous le répétons, entièrement normal.

Hypertension artérielle modérée.

Analyses (Dr. R. Vidal-Ribas) Sang: Hématies 4,800,000 par mm/c.; Hémoglobine 93 %; valeur globulaire 0,96 %; Formule leucocytaire: neutrophiles segmentés 40 %; noyaux en crosse 5 %; éosinophiles 5 %; basophiles 0 %; lymphocytes 43 %; monocytes 7 %;

glycémie 1.93 grms. pour mille. Sérologie pour la lues: Wassermann, m.k. 2. II et M.b.r. II négatives.

L.c.r.: albumine 0.35 grs. pour mille, globulines négatives, glucose 0,65 grms. pour mille, Wassermann négative, cellules 7 par mm/c.

E.E.G. (Drs. *Vila-Badó* et *Samsó-Dies*): Activité fondamentale de repos type alfa. Abondants rythmes lents du type delta, irréguliers, bilatéraux, prédominants discrètement dans la région temporale droite. Avec l'hyperpnée apparaît une instabilité diffuse du tracé. Pas de signes focaux.

TRAITEMENT

Le patient a essayé un traitement anti-infectieux et anti-inflammatoire avec auréomycine, cytotropine, sulmetin, etc.

Il a pris aussi, suivant l'habitude, des doses élevées de tyamine.

EVOLUTION

Le syndrome décrit a suivi jusqu'à ce jour une évolution lente et partiellement régressive. Fin Août il ne souffre déjà plus du hoquet et la dystonie et les troubles sensitifs etc., sont moins accentués.

Du point de vue clinique notre observation se résume, donc, sous les traits suivants:

Un jeune homme de 19 ans, un mois après avoir souffert d'une période de blépharospasme unilatéral gauche, vit s'instaurer dans le terme d'une semaine — accompagné d'un hoquet, violent durant les premiers jours et d'un état fiévreux — un syndrome hémilatéral gauche composé par:

A) — *Symptômes sensitifs*:

- 1 — Subjectivement: paresthésies, avec sensation de constriction thoracique. Pas de douleurs.
- 2 — Objectivement: a) hypoesthésie superficielle, irrégulière, prédominant franchement pour les sensibilités thermiques; b) troubles de l'arthrocinétique; c) astéroesthésie; d) abolition de la sensibilité vibratoire. Pas d'hyperpathie.

B) — *Symptômes extra-pyramidaux*:

- 1 — Dystonie d'attitude de la main.
- 2 — Légers mouvements athétosiques au niveau de celle-ci.

3 – Nous pouvons également considérer ici les faibles syncinésies d'imitation de l'extrémité supérieure.

C) – *Symptômes cérébelleux*:

1 – Tremblement et oscillations au doigt-nez et talon-genou.

2 – Légère dysdiadococinésie douteuse.

3 – Passivité augmentée dans l'extrémité supérieure.

D) Comme caractères négatifs il faut détacher – en plus de l'absence de douleurs et d'hyperpathie – le manque de troubles dans le système pyramidal et la normalité du champ visuel, l'absence concrète d'hémianopsie.

En plus des symptômes indiqués, il souffrait, seulement dans les premiers jours, d'insomnie, se réveillant souvent, de céphalée et d'une sensation de « tête lourde », comme du vertige.

L'évolution du syndrome fut lentement régressive.

Un syndrome de ce type permet un diagnostic topographique bien précis: il traduit une lésion située dans la région subthalamique et pédonculaire supérieure, du côté opposé, en ce cas le côté droit. On peut parler d'un *syndrome rubro-subthalamique* dans le sens de syndrome supérieur du noyau rouge.

L'absence de douleurs et d'hyperpathie, comme autres caractères du syndrome sensitif objectif, permettent d'éliminer le syndrome thalamique classique de Dejerine et Roussy. L'absence d'hémianopsie, la modération de la dyskinésie, permettent d'écarter le syndrome du carrefour hypothalamique décrit par Guillain, Alajouanine et Mathieu. L'absence de participation paralytique du III élimine facilement le syndrome inférieur et alterne du noyau rouge, dans les deux formes de Benedikt et de Claude, codifiées par *Souques, Crouzon et Bertrand*.

Les caractéristiques symptomatologiques d'un tel syndrome rubro-subthalamique comme celui qui nous occupe, furent déjà bien précisées dans les travaux parus à partir de 1920 dus principalement aux cliniciens français: *Roussy, Foix, Laignel-Lavastine* et leurs respectifs collaborateurs. On distingua deux formes différenciées par le nombre supérieur de symptômes cérébelleux dans l'une et des phénomènes hypercinétiques dans l'autre. Quelques unes des photographies de la main affectée de dystonie qui accompagnent les expositions cliniques de ces auteurs classiques, montrent un aspect très semblable, presque identique, de celui correspondant à la main de notre malade, ici reproduite.

Postérieurement à ces premières descriptions, *Raymond Garcin* contribua à détailler la sémilogie (réflexes du cou, syncinésies, etc.) du syndrome topographique qui nous occupe, se servant d'un cas particulièrement fleuri.

D'autre part, nous rappelant les orientations de l'Ecole de *Pierre Marie*, nous pourrions situer certains syndromes rubro-subthalamiques, particulièrement les formes avec composante cérébelleuse bien manifeste, parmi les variantes cliniques de l'« hémiplégie cérébelleuse supérieure » que cet auteur décrit avec *Ch. Foix* et *Thiers*.

Tout ceci en nous référant à des conceptions établies pendant une ère importante et bien définie – qu'aujourd'hui nous dénommons classique – de la clinique neurologique, ère qui connut déjà les apports du Prof. *Knud Krabbe*.

Donc, du point de vue syndromique notre observation s'écarte peu des profils bien définis.

On ne peut parler ainsi du point de vue étiologique. Le syndrome rubro-subthalamique, en effet, reconnaît la plupart des fois, une origine vasculaire. Dans notre cas, l'occurrence préalable d'un blépharospasme accompagné sûrement d'autres clonies faciales, la présentation simultanée de fièvre, de hoquet, etc., appuient décidément – depuis le terrain clinique – la nature encéphalitique du processus. Les légères modifications du l.c.r. (hyperalbuminose et hyperglucorachie modérées) appuient aussi cette même orientation.

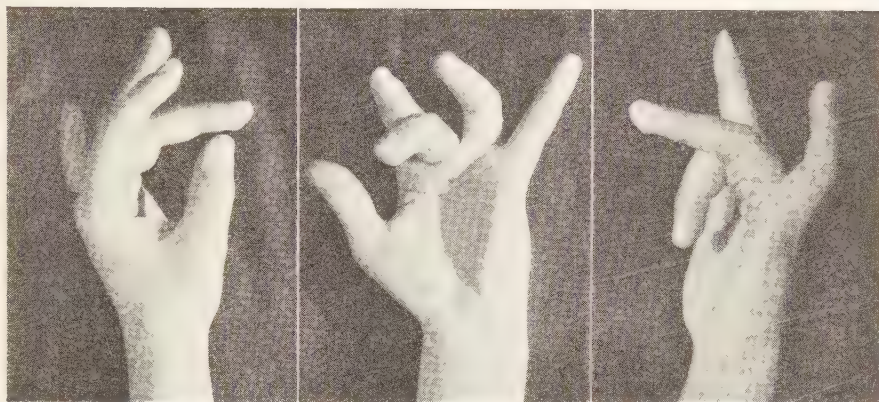
Il n'est guère courant de voir un processus encéphalitique adopter l'expression clinique d'un foyer lésionnel aussi localisé.

Des troubles du sommeil importants ne se présentèrent pas, du moins dans le sens d'une hypersomnie. Un sommeil quelque peu difficile seulement, réveillant le patient subitement et facilement.

Il n'y eut pas non plus de troubles de la motilité oculaire extrinsèque ni intrinsèque. Nous voulons rappeler ici les apports que *Knud Krabbe* fit il y a une trentaine d'années à la sémiologie pupillaire de l'encéphalite épidémique.

Du point de vue nosologique, notre observation peut rappeler le problème, encore d'actualité, des formes cliniques de cette encéphalite « épidémique » ou « léthargique » et de ses limites. Dans notre cas le syndrome obéit fondamentalement à une lésion des voies blanches et non des groupements neuronaux.

Du point de vue physiopathologique et pathogénique, la pathologie de la région subthalamique et de la calotte pédonculaire nous oblige à aller à la recherche des corrélations qui peuvent exister entre les faits cliniques, d'une part, et les données anatomo-fonctionnelles relatives à la substance réticulée du tronc cérébral supérieur et aux projections axonales qui le parcourent, d'autre part.



Malgré les nombreux travaux et les discussions qu'elle a suscités, l'interprétation physiopathologique de la sémiologie extrapyramidale continue à être obscure et peu connue. La clinique nous montre ici une variété de troubles toniques, dyskinétiques, réflexes, etc., qui ne trouvent pas une équivalence ni une explication satisfaisantes dans le terrain expérimental.

Nous ne nous proposons pas de réviser ici, même sommairement, cette question en ses multiples aspects.

Mais nous voulons rappeler les nouvelles connaissances relatives à l'anatomie et à la physiopathologie de la substance réticulée du tronc cérébral supérieur, que nous devons principalement à *Horace W. Magoun* et à ses collaborateurs.

Nous savons par ces travaux, que dans cette région supérieure de la substance réticulée on trouve deux importants systèmes, tous les deux plurineuraux et multisynaptiques. Il s'agit d'un système ascendant activateur, qui à travers le diencephale contribue puissamment à maintenir la force et le rythme de l'activité fonctionnelle de l'écorce cérébrale, et d'un système descendant facilitateur des réponses réflexes myo-thatiques, du réflexe de traction. Les relations de ce dernier système avec la multitude des projections dénommées depuis longtemps extra-pyramidales sont étroites, mais ne sont pas encore bien précisées.

Il est douteux que les difficultés du sommeil (disons les insomnies) présentées par notre patient puissent avoir un rapport avec une irritation temporaire du système activant ascendant.

Mais il est probable que la diminution des réflexes profonds dans les extrémités supérieures, totalement inapparents dans la gauche, ait à voir avec l'atteinte parcellaire du système descendant facilitateur.

Dans des travaux récents, l'un de nous (L. B.-B.) a suggéré que

l'atteinte diffuse de ce système joue très probablement un rôle important dans le genèse de la paraplégie en flexion d'origine cérébrale type Alajouanine.

Les corrélations des aspects cliniques avec les mécanismes physiopathologiques suscitent encore au niveau de la région à laquelle nous nous référons, d'autres problèmes nombreux.

Jusqu'à quel niveau peut être suivie sémiologiquement et interprétée physiopathologiquement, suivant les méthodes connues, l'atteinte du faisceau ascendant dérivé du pédoncule cérébelleux supérieur, le long de son trajet mésencéphalo-thalamo-cortical? Voici une question pleine de cuisantes difficultés dans le sein de la neurologie actuelle.

Et encore plus concrètement: jusqu'à quel niveau peut se manifester et prévaloir cette modification concrète du tonus musculaire que nous dénommons avec *André-Thomas* passivité? On comprend facilement que la pathologie de la région rubro-subthalamique, associant une physiopathologie extrapyramidale à une physiopathologie cérébelleuse, puisse conditionner des modifications très variées du tonus musculaire, dont la description sémiologique peut être tentée en suivant les sillons marqués patiemment et de manière géniale par le grand clinicien français, mais dont l'interprétation physiopathologique est encore pleine de lacunes. Même l'hypertonie plastique extrapyramidale, pure et précise, dont *Foix, Chavany, Thévenard*, etc., contribuèrent à fixer la sémiologie, ne possède pas encore, nous insistons, une interprétation physiopathologique suffisante.

En ce qui concerne les lésions rubriques, les modifications distinctes du tonus appréciables dans les deux variétés syndromiques de Benedikt et de Claude peuvent s'interpréter comme traduisant l'atteinte inégale des projections extrapyramidales et cérébello-corticales, une des deux prédominant dans chaque cas. Mais cette suggestion logique n'épuise pas la discussion physiopathologique de ces tableaux cliniques.

Trelles a introduit une note intéressante dans l'interprétation de tels tableaux, en faisant observer que, tandis que le syndrome de Benedikt est plus fréquent dans l'enfance (*Lhermitte*), celui de Claude se présente électivement à un âge plus avancé. Cela peut suggérer une modification possible — restriction ou amplification — de la valeur fonctionnelle relative de quelques-uns des systèmes atteints au cours de la maturation individuelle.

Détaillant la sémiologie du tonus dans les lésions rubriques, deux cliniciens de l'École de la Pitié, *Chavany* et *Thiebaut*, décrivirent la présentation d'une hypotonie de fond sur laquelle apparaissait une hy-

pertonic accessoire. Ce fait a été corroboré par son collègue *Krebs* pour le cas de quelques lésions encéphalitiques plus diffuses.

D'autre part, des neurophysiologistes de la catégorie de *Ingram* et *Ranson* ont insisté depuis longtemps déjà sur le fait que le rôle assigné au noyau rouge dans la régulation de posture est joué, au moins en grande partie, par d'autres portions de la formation réticulée supérieure. Ces auteurs concluent de plus que « puisque le noyau rouge paraît participer à la régulation du tonus, sa désignation classique comme un centre pour la transmission et sélection d'influx cérébelleux, corticaux et palidaux actionnant sur la voie terminale commune peut être considérée encore comme éminemment raisonnable ».

L'expression clinique cérébelleuse des lésions rubriques ne paraît pas embrasser de même manière toute la sémilogie cérébelleuse classique: celle de *Babinski*, d'*André-Thomas* et de *Gordon-Holmes*. En effet, *Chiray*, *Foir* et *Nicolesco* et *Chavany* et *Thiebaut* ont fait ressortir, en ces cas, la prédominance du tremblement sur les autres symptômes cérébelleux.

En nous référant à d'autres questions posées par l'observation clinique que nous relatons ici, nous voulons faire constater les difficultés d'interprétation physiopathologique qu'entraîne cette dystonie d'attitude particulière qu'est la main subthalamique. L'analyse du tonus musculaire des petits muscles de la main, l'étude de ses fines adaptations réflexes, de son registre électromyographique, l'évaluation des troubles associés de la sensibilité profonde, etc., pourraient éclaircir peu à peu cet attrayant problème, nettement clinique.

Nous rappelons ici en passant, l'apparition transitoire d'une « main thalamique » au cours des expériences d'exploration élective sur des structures subcorticales en neurochirurgie, menées à bout par *David* avec *Talairach*, etc.

Le blépharospasme de notre patient, associé sans doute à d'autres clonies faciales, doit s'interpréter probablement comme une manifestation supranucléaire extrapyramidale.

Son caractère homolatéral au syndrome présenté ultérieurement le démontre ainsi.

Nous dirons que nous sommes en pleine époque d'étude physiopathologique des myoclonies, subséquente à l'analyse clinique de celles-ci faite par *Krebs*, *van Bogaert*, *Radermecker*, etc.

Nous voulons stipuler que nous ne croyons pas que la présence chez notre malade d'une aréflexie cutanée abdominale unilatérale, associée à des troubles sensitifs, etc., autorise à parler d'une sémilogie pyramidale.

Le carrefour extrapyramidal constitué dans la région pédonculo-

subthalamique comprend donc, évidemment, une multitude d'intégrations de la plus haute importance, insuffisamment connues encore, en relation avec le tonus de posture, avec le tonus d'attitude, etc. Il importe donc de poursuivre l'étude de ses altérations sur le plan clinique avec toute la minutie de la meilleure sémiologie. Les apports expérimentaux, même s'ils sont de grande valeur, pourront rarement arriver à produire dans cette région des phénomènes dont la corrélation avec la clinique se montre claire et immédiate. Il conviendra, par conséquent, en recueillant ces intéressants apports, d'avoir présent à l'esprit que, comme l'a écrit *van Bogaert* dans la préface à la Monographie dédiée au Système Pyramidal par l'un de nous (L. B.-B.), « l'expérience physiologique ne s'intéresse souvent gu'à un maillon de cette chaîne qu'est toujours, chez nous, le syndrome ».

Nous dirons pour terminer que les altérations E.E.G. recueillies dans notre cas, pourraient traduire les modifications produites par la lésion dans les régulations diencéphalo-mésencéphaliques ascendantes.

Ce que nous venons de montrer et de commenter sur la continuité ininterrompue des efforts que doit déployer la neurologie clinique, doit nous rappeler l'exemple du Professeur *Knud H. Krabbe* qui s'y est attaché toute sa vie durant.

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METHODS USED TO ELICIT OR ACCENTUATE ABNORMALITIES IN THE ELECTROENCEPHALOGRAM OF EPILEPTICS

A Brief Review

By

KARL G. BENTSEN

It is generally stated that more than 80 per cent of epileptics have abnormal interseizure electroencephalograms, but in routine E.E.G. less than 30 per cent show paroxysmal abnormalities or seizure discharges which are helpful in establishing a diagnosis of epilepsy (*Gibbs, Gibbs and Lennox* 1943). In order to elicit such E.E.G.-discharges various techniques have been devised, some of them being useful in revealing focal abnormalities as well.

The chief methods used are hyperventilation, sleep, Metrazol injection, photic stimulation, and photo-Metrazol activation.

Hyperventilation may elicit grand mal but is less effective than other methods in that respect. 77 per cent of the patients with petit mal epilepsy exhibit 3 per sec. bilateral synchronous wave-and-spike formations but with hyperventilation 8 per cent in addition show these formations (*Gibbs, Gibbs and Lennox* 1936 and 1943), and in those patients hyperventilation produces the wave-and-spike-pattern more frequently than in any other group.

In 500 patients with epilepsy *Gibbs and Gibbs* (1946) found seizure discharges during light sleep in 82 per cent as compared with 36 per cent while awake. In particular petit mal variant discharges increase highly and in some cases they appear only in sleep, but also petit mal and both types of grand mal discharges will be precipitated during sleep. In patients suffering from "psychomotor seizures" only, waking records showed seizure discharges in 25 per cent. During sleep 97 per cent had such discharges and 88 per cent had focal seizure discharges in the anterior temporal region.

Metrazol in sufficient quantity may produce seizure discharges and

convulsions in normal persons. It has been shown, however, that epileptics in that respect generally have a lower threshold to Metrazol than have normals and other patients. *Ziskind* and *Bercel* 1946 with a slow injection technique observed occurrence of 4-5 per sec. waves in 25 epileptics with an average dose of 230 mg. The corresponding average dose for 11 controls was 340 mg. Using an intermittent rapid injection technique (max. 300-350 mg) *Buchthal* and *M. Lennox* (1953) in 682 normal persons (age 17-24) found Metrazol induced paroxysms in 15 per cent of subjects with a normal E.E.G., in 32 per cent of those with a borderline, and in 50 per cent of those with a paroxysmal pre-Metrazol E.E.G. In 57 epileptics who had normal routine E.E.G. *Merlin*, *Henriksen* and *Grossmann* 1950 evoked seizure discharges in 47 per cent, using a very slow intravenous infusion of Metrazol. In 38 controls no seizure discharges were observed. In addition they found that evoked rhythmic repetitive discharges were characteristic of patients with "idiopathic" epilepsy, whereas arrhythmic, asymmetric discharges characterized the group classified as symptomatic epilepsy. After intermittent, rapid injection of max. 350 mg Metrazol *Fuglsang-Frederiksen* (1952) in 96 idiopathic and symptomatic epileptics, 86 of whom had normal or borderline E.E.G., elicited characteristic E.E.G. paroxysms in 82 per cent. In 68 per cent of 75 patients suffering from syncopal spells such discharges were also called forth by Metrazol, but only in 1.6 per cent of 63 controls. In 1948 *Cure*, *Rasmussen* and *Jasper* in 80 per cent of a heterogeneous group of epileptics observed E.E.G. discharges of the epileptic type, when using a slow injection technique (max. 400 mg). 26 per cent of their controls showed bilateral synchronous 4-6 per sec. waves.

By intermittent photic stimulation *Buchthal* and *M. Lennox* in a large group of normal persons (aged 17-24) with normal or borderline E.E.G. elicited E.E.G. paroxysms in 1.6 per cent as compared with 13.5 per cent in a group of 100 patients with grand mal epilepsy. *V. J. Walter* and *Grey Walter* state that the responses in epileptics are abnormal in about 30 per cent of all cases, two thirds of those with evoked abnormalities showing nothing specifically epileptic in routine E.E.G. or during overbreathing. According to *Gastaut* photic stimulation produces specific E.E.G. abnormalities in 10-20 per cent of these patients.

Photo-Metrazol activation combines the lowered threshold for seizure discharges in certain patients, especially epileptics, with the eliciting effect of photic stimulation. The method is not quite specific. Patients with psychomotor epilepsy and epileptics with a cortical focus commonly have a high threshold.

To sum up: it may be said that among the practicable activation methods sleep and intravenous Metrazol injection at present must be regarded as the most effective and perspicuous ones in adults. The results of the Metrazol method can now be evaluated with more certainty when they are compared with the normal figures of *Buchthal* and *Lennox*, provided that exactly the same technique be employed.

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MYOPATHIA DISTALIS JUVENILIS HEREDITARIA

By

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Knud Krabbe, to whom this study is dedicated as a token of high regard, in 1930 described the case-histories of two middle-aged sisters showing a progressive paresis of both legs of a few years' standing. Biopsy examination (calf-muscle) revealed a distinct myopathia. Not only the late occurrence, but also mainly the distal localization of the process, in these cases were striking phenomena.

The term distal myopathia was used for the first time by *Gowers*, who in 1902 described a young man, 18 years of age, in whom a slowly progressive paresis had developed in both feet, later also in both hands, starting at the age of 10 or 11 years. On examination the flexors of feet and toes appeared to be completely paralytic and greatly atrophic, whereas the likewise atrophic extensors of feet and toes still showed a weak function. There were no sensibility disturbances, no fascicular contractions and no symptoms of an electric degeneration reaction. Hands and fore-arms showed an analogous picture, though less advanced. The proximal muscle groups (thighs, upper arms, trunk) were normally developed. However, in the neck the sternocleidomastoid muscle appeared to be almost absent on both sides, the facial musculature likewise being insufficiently developed. Consequently there existed actually a predominantly distal myopathia, which, however, owing to the neck and head musculature being affected as well, showed a distinct relationship with the facio-scapulo-humeral type of progressive muscular dystrophy, as already well-known at the time.

Since 1902 various other cases of myopathia with a more or less distal localization have been reported in the literature. It is not intended here to analyze all these, this having been done already elsewhere (see below). The impression is obtained that the cases presented in the literature up to 1952 as distal myopathia may all be included in three groups. First, there are atypical cases of progressive muscular

dystrophy with initially a distal localization, in which, however, in the further course also the facial, neck, and shoulder muscles become involved in the process. In addition to the patient of *Gowers*, a similarly typical example of this group is the family described in 1943 by *Milhorat* and *Wolff*, of which twelve members had been affected, distributed among three generations. It is true that the myopathia showed a distal onset (in one case affirmed at autopsy), but after a few years extended to proximal muscle groups.

A second group of cases belongs to the clinical picture of atrophic myotonia, in which the myotonic symptoms become manifest in the latter stage of the disease only. A typical example of this group appears to be the case described by *Ley* and *Titeca* in 1933, of two brothers, who were suffering from cataract in addition to distal myopathia.

Finally, in a third group distal myopathia appears in fact to be based on a neurogenic muscle atrophy, in which sensibility disturbances, as is known, may be entirely lacking for many years. This differential diagnosis may be prevented further by the fact that in neurogenic muscle atrophy the muscular weakness in various cases appeared to occur in the hands at the same time as in the legs below the knees, or even earlier. A typical example of this a.o. is the patient described by *Pette* (1921), with an extensive post-mortem examination. Whether the above-cited observation of *Knud Krabbe* must be included among these, remains an open question, since only biopsy examination was performed. In disfavour of the diagnosis myopathia, as drawn, appears the fact that distinct sensibility disturbances were found in one of the patients.

This then was the position up to 1951, when *Welander* in Stockholm published a monograph, titled: *Myopathia distalis tarda hereditaria*, in which an extensive discussion of the literature is given as well. In this study no less than 249 patients, showing typical distal myopathia, are described. Of these, 149 were male and 100 were female, all resident in Sweden and belonging to 72 genealogical trees. A typical dominant heredity could be demonstrated in nearly all cases. In the great majority of cases the disease developed between the 40th and 60th year of age and in 89 % of the cases started with weakness and wasting of the small hand muscles, the musculature of the leg below the knee and of the foot being afflicted somewhat later. The course mostly was very slowly progressive. Fascicular contractions were not clearly observed, nor were sensibility disturbances. In no case an electric degeneration reaction was established, whereas the electromyographical examination definitely pointed to a primary muscular disease. This was confirmed by pathological examination (24 biopsies). By means of

three post-mortem cases it could be shown that the central and peripheral nervous system had not been involved in the process.

By the investigations of *Welander* it has now irrefutably been established that, at least in Sweden, indeed, distal myopathia occurs as a familial hereditary syndrome. It has appeared to me that in Holland likewise a genuine distal myopathia occurs as a familial heredi-

PEDIGREE OF THE FAMILY Z.

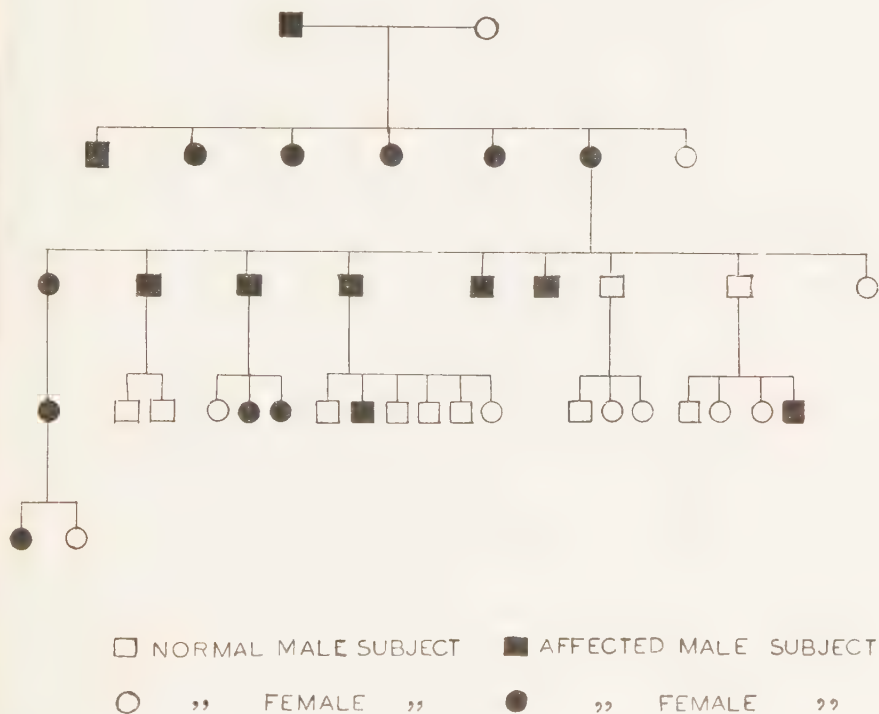


Fig. 1.

tary disease. The first report was made by me in November 1953 (meeting of the Society of Neurologists at Amsterdam). The various sufferers all appeared to belong to a single family, the members of which nearly all are resident in North Holland. Owing to the great help of Dr. *Roskam* (Winkel, North Holland) an extensive family-tree could be drawn up (Fig. 1). The very characteristic clinical picture was so well known to most members of the family, that sufficiently reliable data could be obtained concerning previous generations as well. As far as the data go, 19 members of the family, distributed among 5 genera-

tions, were affected by the disease. Of these, 9 patients were neurologically examined, of one of whom post-mortem examination could be performed later. The clinical picture showed an almost identical course in all. Now the clinical descriptions are given first, subsequently the discussion of the anatomical examination.



Fig. 2.
Distal myopathy (case 1).

No. 1. L. Z. male, born 19-2-1890, was examined by myself for the first time on January 1953. He was admitted to the Neurological Clinic on 16. March 1953, where he died on 22. March 1953. The history mentioned that at the age of 12 or 13 years he was for the first time slightly troubled by muscular weakness, which revealed itself in both hands and feet nearly at the same time. In the following years the paresis increased very slowly, gradually atrophy of hands and the lower part of the legs developed. The patient especially in cold weather was less able to use his hands. He gradually began to show a "cock's stride", he did not notice spontaneous contractions in the wasted muscular areas, never experienced pain and never complained of "deaf" sensations. As he appeared incapable of farm labour, his original destination, he was trained to be a baker. In spite of gradually increasing motor disturbances he was able to perform this work, including distribution of the bread, till medio 1952. He then had to discontinue this. At the age of 36 he suffered from rheumatic polyarthritis, from which he would have kept a heart failure. Subse-

quently he now and then had mild complaints of an oppression in the chest for which he was repeatedly treated and given drugs. The last year these complaints increased. On neurological examination the principal abnormality was found to be a very marked muscular atrophy of hands, forearms, feet, and legs below the knees (Fig. 2). The disorder was approximately symmetrical. Thenar, hypothenar and interosseous muscles had almost completely wasted on both sides, as had the

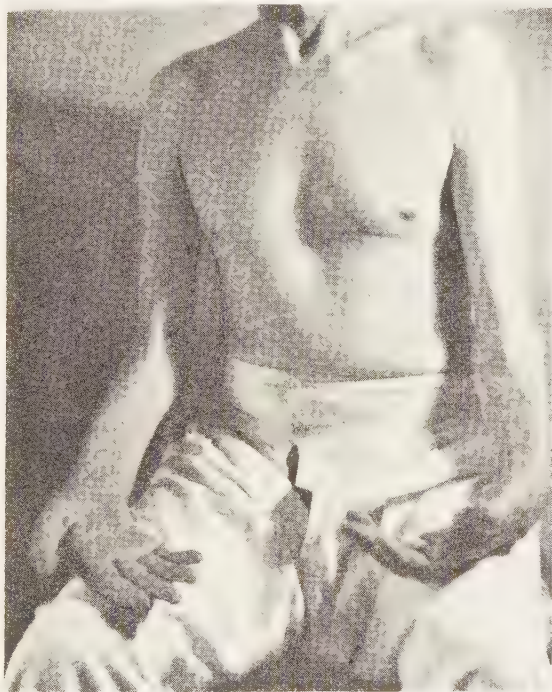


Fig. 3.
Distal myopathy (case 3).

muscles of the foot and the lower part of the leg. On both sides he showed arched feet. Spreading the fingers was impossible, as was opposition and abduction of thumbs and little fingers. Very feeble flexion and extension of the fingers were still possible on both sides. Movements of the wrist joint were not possible on the left, very slightly possible on the right. Flexion and extension in the elbow joint were slightly impaired, especially on the left. The movements in the shoulder joints were normal. Feet and toes were paralytic on both sides. The movements of the knee joints were possible but impaired on both sides. The movement of the hip joints were normal on both sides, as were those of trunk and neck musculature. The facial, tongue, and throat musculature showed no abnormality at all. The patient was able to sit, to stand up, and to walk with the help of a stick. He was reasonably able to rise from the recumbent and sitting positions. In the atrophic muscles no fascicular contractions were visible. The arm reflexes, abdominal and patellar reflexes could all be easily elicited, and were alike on left and right. The Achilles



Fig. 1.

Normal anterior horn motor cells (cervical part of the spinal cord; Nissl stain).

tendon reflexes were lacking, as were the plantar reflexes. The sensibility in all areas was completely intact. The pupillar reflexes and ocular movements were undisturbed. The visus on both sides was 1, there was no hemianopsia, the eye-fundus on both sides was intact. On electrical examination signs of E.D.R. were nowhere found, only a marked decrease, or even absence of excitability in the affected muscles. The cerebrospinal fluid showed a normal pressure and composition. On internal examination a distinct cardiac dysfunction appeared to exist: there was slight dyspnoea and cyanosis, the pulse was irregular, the heart was clearly enlarged towards the left, while the electrocardiogram indicated the existence of auricular fibrillation. On 20 March 1953 the patient ran a temperature and developed increasing dyspnoea. Distinct abnormalities were established in the lungs. Notwithstanding the application of antibiotics the patient died on 22 March. At autopsy (Institute of Pathology, head: Prof. *H. T. Deelman*, M.D.), in addition to an extensive muscular atrophy the following abnormalities were found: hypertrophy of the heart, wide pulmonary arteries, patent foramen ovale, bilateral bronchopneumonia, and scarifications in both kidneys (presumably in consequence of an embolic process). The brain, spinal cord, various peripheral arm and leg nerves, and several pieces from muscles of the thigh and the leg below the knee were handed over to the Neuropathological Laboratory of the Neurological Clinic for further examination. The report concerning those is given below.

No. 2. W. Z., male, 36 years old, a son of no. 1, likewise was examined for the first time on 14 January 1953. This patient already at the age of 5 or 6 years was gradually troubled by a condition of weakness of both hand and feet, slowly progressive in the course of the years. In view of his partial invalidity he likewise chose the baker's trade. He has been able to perform his work as a baker and

bread distributor almost normally up till low. On examination a symmetrical atrophy and paresis appeared to exist in all small hand muscles, among which the thenar and interosseous muscles showed the most pronounced functional disturbance. The extensors and flexors of the wrist also appeared to be paretic. However, the movements of elbow and shoulder joints were executed with adequate strength. Upper arms and shoulder girdle did not show a trace of muscular atrophy. In the legs a situation existed corresponding to that in the arms. The muscles of



Fig. 5.

Left gastrocnemius muscle; van Gieson-stain; almost complete atrophy.

the feet and legs below the knee were atrophic and paretic. The dorsal flexion of feet and toes appeared to have lost strength to approximately the same degree as the plantar flexion. No fascicular contractions were visible, not after injection of $\frac{1}{2}$ mg prostigmine, either. The sensibility was entirely intact. The arm reflexes were present, as were the abdominal and patellar reflexes. The Achilles tendon reflexes were lost. The plantar reflexes were normal. Other abnormalities were not established; the musculature of neck and face appeared to function normally. On electrical examination of the paretic muscles signs of E.D.R. were nowhere found; however, the excitability appeared to have decreased quantitatively to a considerable degree. An electromyogram was made of a few muscles, in which a decreased amplitude only of the action potentials could be determined. There were no fibrillations visible.

No. 3. K. Z., male, 72 years of age, brother of no. 1, uncle of no. 2, was likewise troubled for the first time when 5 or 6 years old. His complaints were entirely similar to those of his brother and nephew. According to the patient the disease

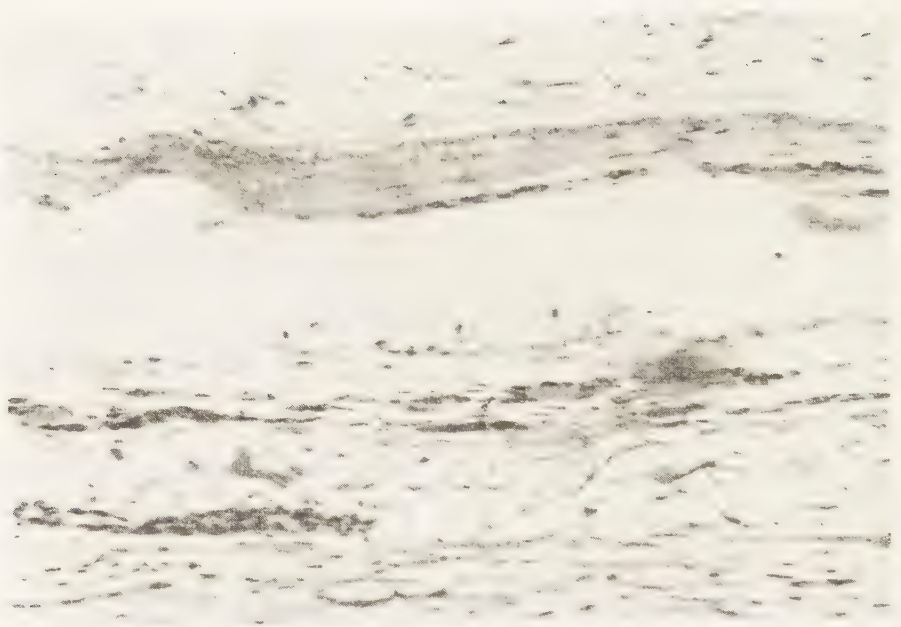


Fig. 6.

Atrophy of the left tibialis anterior muscle (haematoxylin-eosin).

has not progressed notably after his 50th year. He has regularly performed his work as a baker up to his 55th year. He subsequently retired. On examination also in this case a symmetrical, pronounced atrophy of both forearms, hands (Fig. 3) and legs below the knee appeared to exist. The hands were almost, the feet completely, paralytic. Nevertheless the patient appeared to be able to walk without support, owing to the use of high lace-shoes. The sensibility also in this patient was completely intact. The biceps and triceps reflexes remained, as did the patellar reflexes. The Achilles tendon reflexes were lost. On electrical examination it appeared that the greatly atrophied paralytic muscles could no longer be made to contract. The excitability of the paretic muscles was greatly reduced. There were no signs of E.D.R., however. Fascicular contractions were absent. No electromyographical examination was performed.

No. 4. Mrs. N.-Z., 75 years old, was examined in the summer of 1954. She started to have complaints when approximately 13 years of age, first having troubles when milking and skating. Also in this case the symptoms gradually increased till the age of approximately 50 years. This patient also showed the typical picture of a purely distal myopathia of almost symmetrical character. At this time she is still able to walk without support. Of the reflexes only those of the Achilles tendons were lacking.

No. 5. Mrs. M.-N., 54 years old, was likewise examined in the summer of 1954. In contrast to the other patients she stated emphatically that her complaints, in hands as well as in feet, had not started until she was approximately 30 years old, but had gradually increased since then. She likewise shows the typical picture of

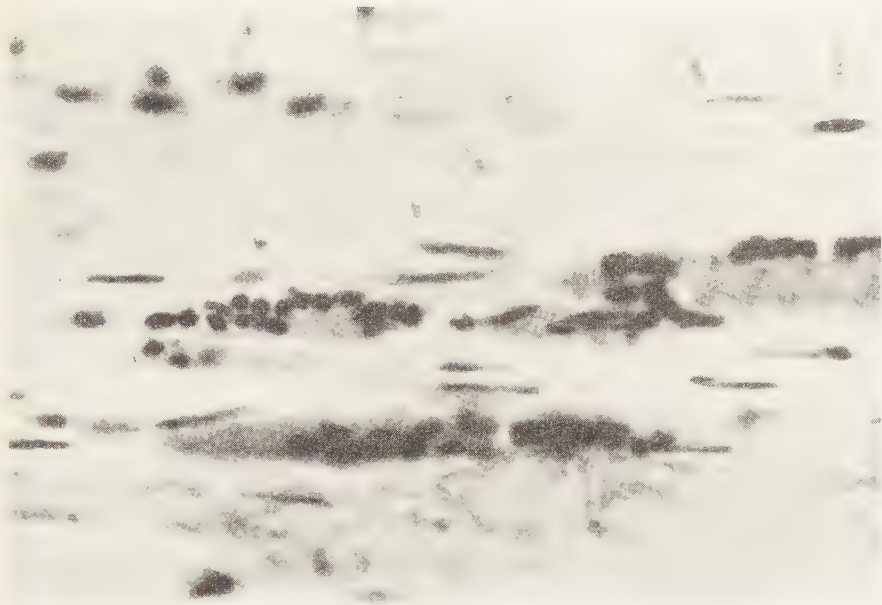


Fig. 7.

Proliferation of the sarcolemma nuclei (left tibialis anterior muscle; haematoxylin-eosin).

distal myopathia, in which, however, the symptoms were less pronounced than in the other cases. The Achilles tendon reflexes were lacking also in this patient.

No. 6. Miss M., 21 years old, examined in the summer of 1954. When at the age of 14 noticed for the first time that her hands grew less strong. One year later the paresis also developed in the feet. On examination she likewise showed the typical picture. Apparently the dysfunction was more progressive than in her mother (no. 5), for she showed a distinctly worse gait. The Achilles tendon reflexes were lacking, the other reflexes could be evoked normally.

No. 7. J. Z. Senior, male, 65 years of age, a market-gardener, was examined in the summer of 1953. When 16 or 17 years old, he for the first time noticed that he possessed insufficient strength in his hands when milking. At approximately the same time the feet became somewhat weaker. Since then the symptoms were gradually progressive till the age of about 50 years, after which the condition became stationary. Objectively: typical distal myopathia. He is still engaged in his occupation. The Achilles tendon reflexes could not be elicited.

No. 8. J. Z. Junior, male, 43 years old, running camp-sites. Till his 14th or 15th year the members of his family thought that he would not develop the dreaded disease. However, he himself at that time had already noticed that he was less able to skate than those of the same age. Shortly afterwards also his hands grew weaker. A slow progression occurred to the approximate age of 40. Since then the disease has appeared stationary. On examination in the summer of 1953, also in this case a distal myopathia appeared to exist, in a rather mild form. It may be

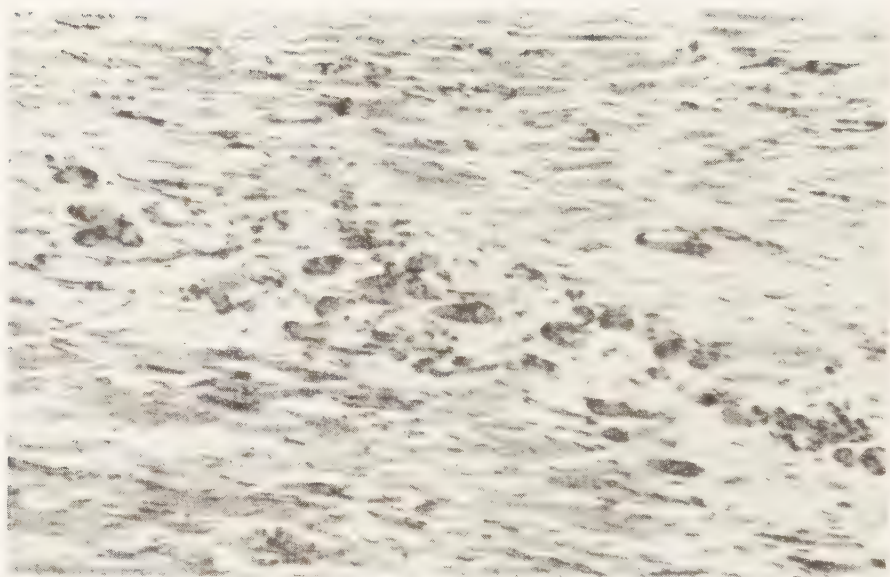


Fig. 8.

Muscle giant cells in atrophic left tibialis anterior muscle (haematoxylin-eosin).

mentioned as a peculiarity that in this patient in the well-developed upper arms and thighs spontaneous contractions (myokimias?) were observed now and then. The Achilles tendon reflexes were lacking.

No. 9. Mrs. B.-Z., 27 years old, obtained her first complaints when 10 years of age. On examination (summer 1953) she likewise appeared to show the typical picture. Not a single movement was completely lost. The disorder allegedly showed only a very slow progression. The Achilles tendon reflexes were lacking.

ANATOMICAL EXAMINATION

The following results were obtained on anatomical investigation of the nervous system and the muscular tissue of the first-described patient.

In the *brain* in the left 3rd frontal gyrus a small, superficial, brown, a few cm long, band-like focus of softening was found, obviously of vascular origin and without connection with the muscular disorder. Otherwise, no macroscopically visible abnormalities were found, neither in the cerebrum nor in the cerebellum and brain stem. Further microscopical examination of the brain stem revealed that the various motor nuclei showed a normal configuration. Concerning the *spinal cord*, pieces were excised from the cervical, thoracic, and lumbosacral portions, and examined by means of serial staining methods (Weigert

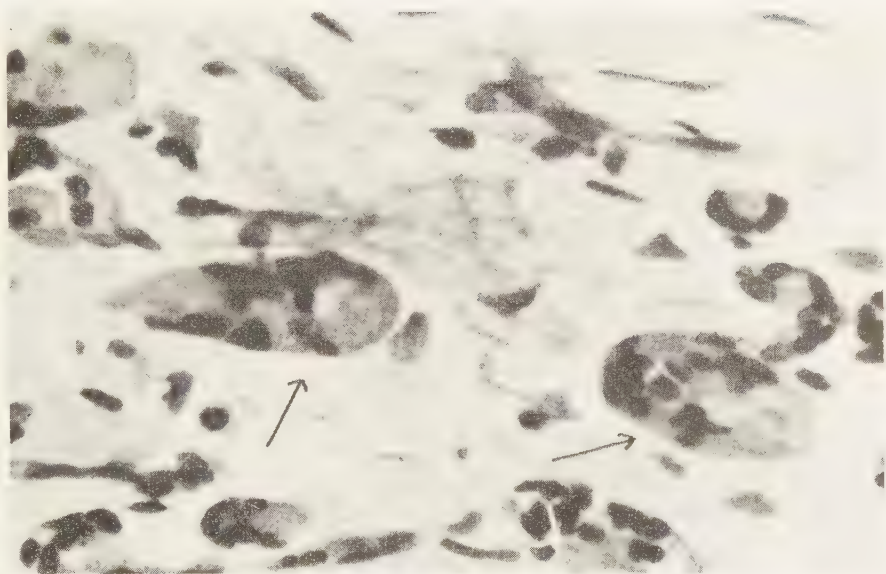


Fig. 9.

Muscle giant cells by higher power magnification.

Pal, Nissl, Holzer, haematoxylin-eosin, Bielschowsky). No abnormality at all was found, neither in the anterior horn motor cells (Fig. 4), nor in the various fibre systems. The anterior and posterior roots also showed a normal aspect. On the other hand the *muscles* examined (left and right anterior tibialis muscles, left and right gastrocnemius muscles, left and right rectus femoris muscles) showed severe changes, especially as regards both first-mentioned muscles. Staining was performed with haematoxylin-eosin, according to Van Gieson, and according to Bielschowsky. *In both gastrocnemius muscles hardly anything resembling muscular tissue could be found; in the tibialis anterior muscles remnants only.* Everywhere the muscle tissue had been exchanged for connective tissue, and now and then also for fatty tissue (Fig. 5 and 6). There was a distinct proliferation of the sarcolemma nuclei, presenting themselves neatly in rows between the completely, or largely, degenerated muscle fibres (Fig. 7). Now and then distinct muscle giant cells were found (Figs. 8 and 9). In so far as present, the muscle fibres clearly showed vacuolization, narrowing, and "splintering", and mostly loss of the cross-striation as well. Around the vessels also distinct connective tissue proliferation was found. In these areas also existed a physiological—in view of the age—arteriosclerosis and phlebosclerosis. Nowhere inflammation symptoms were seen. As re-

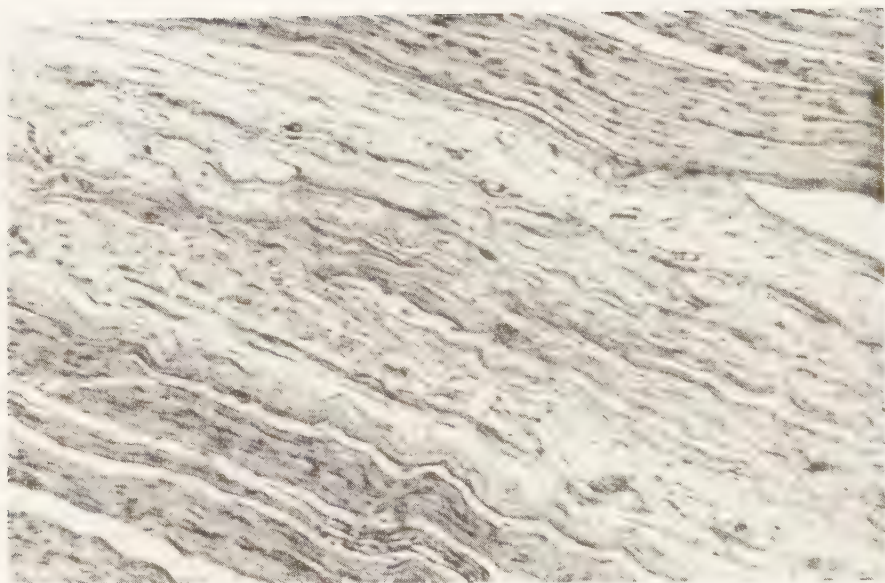


Fig. 10.

Slight increase of connective tissue between the new fibres of the right sciatic nerve (haematoxylin-eosin).

gards the proximal muscles, the right rectus femoris showed a normal aspect. In the left rectus femoris muscle on the other hand, atrophic abnormalities were indeed established, to a much less degree than distally, however. The impression was obtained that the few atrophic fibres present, were more or less diffusely scattered in the muscle, in any case concentrated in groups. Finally, both *sciatic nerves* (haematoxylin-eosin, Van Gieson, Weigert Pal, Bielschowsky) were examined. These, at the various levels examined, undoubtedly showed abnormalities, but to a much less degree than the distal muscles. These abnormalities on the one hand consisted of a slight increase of connective tissue between the nerve fibres, whereas on the other hand mild symptoms of nervous degeneration were observable. Since the applied silver stain did not yield a satisfactory result, no detailed opinion as to the condition of the peripheral nerve endings could be expressed. Nevertheless, in view of the findings described above, the conclusion seems justified that here a primary degenerative muscular disorder should be assumed, almost exclusively concerning the distal muscles, so that this may be rightly called *distal myopathy*. The slight alterations in the peripheral nerves may be taken as secondary in the sense of a retrograde degeneration. It is true that similar altera-

tions mostly are not found in progressive muscular dystrophy, but it must be kept in mind that in the anatomically investigated case the disease had existed for at least 50 years, before an intercurrent disease ended life.

SUMMARY AND CONCLUSION

A description is given of a family from North-Holland, in which, distributed among 5 generations, 19 cases of typical distal myopathia occurred. Of these, 9 patients could be examined. The disorder, dominantly hereditary, was characterized by the development of a symmetrical paresis and atrophy of the distal muscle groups of the extremities. In all cases investigated the onset appeared to have been almost simultaneously in hands and feet. The first symptoms become manifest between the 5th and 15th year (in one case about the 30th year). Following a very slowly progressive course, a stationary condition ensues about the 50th year. The muscles of thighs, trunk, upper arms, shoulder girdle, neck, and face, remain normal in volume and function, also after very prolonged duration of the disease. This disorder therefore may be considered to be relatively benign, causing only a very partial invalidity. Of the various tendon and periost reflexes, only those of the Achilles tendons disappear (and at an early time). In all patients examined the sensibility remained completely intact, also in later stages of the disease. On electrical examination no signs of E.D.R. were found, while electromyography (applied to one patient) showed the typical picture of muscular dystrophy. On anatomical examination, performed in one case, no abnormalities appeared to exist in the spinal cord, whereas the examined distal muscles showed extremely severe degenerative changes. Slight, probably secondary, alterations, were observed in both sciatic nerves.

When finally considering the question whether this Dutch family with distal myopathia may be deemed to be equivalent to the Swedish cases described by *Welander*, this question must be answered in the negative, at least for the time being. For there are some characteristic differences. The principal of these is the early onset in the cases described by us, in which the disease appeared to start prior to adult age (5-15 year), with one exception. In addition, it appears significant that in our cases a slow progression existed till approximately the 50th year, with a subsequent stationary condition. It should also be mentioned that the distal flexors and extensors were equally affected, whereas *Welander* reports a distinct preference for the extensors. Finally, in our patients the disease starts simultane-

ously in hands and feet, whereas *Welanders* was able to ascertain that in 89 % of his cases the hands were afflicted first. In view of all these arguments, the cases described above may be taken as an independent clinical unity, to which may be given the name of *myopathia distalis juvenilis hereditaria*.

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THE NEUROHUMORAL BLOOD SUGAR REGULATION UNDER INSULIN HYPOGLYCEMIA IN PATIENTS AFTER SPLANCHNICECTOMY

By

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THE INSULIN TOLERANCE CURVE

If a proper quantity of insulin is administered intravenously to an experimental animal or a patient (in the case of human beings 16–20 units) a characteristic fall in the blood sugar values will be obtained followed by a rise. If the blood sugar values are drawn up in a curve where the time is noted on the abscissa and the blood sugar values on the ordinate an insulin tolerance curve is obtained. This curve has been carefully examined by *Brühl* (4) and by *Fraser and his co-workers* (17).

The insulin tolerance curve in normal men follows a constant and characteristic course. It is marked by a rapid almost lineally initial fall rounded off downwards in a gentle convex arch, the lowest peak of which is reached c. 35 minutes after the time of injection. The ascending part of the curve is less steep and particularly characterized by the fact, that “a bend” is localized at about 50–60 minutes after the injection at a blood sugar value of about 70 mg. per cent. The bend appears when the regeneration of the sugar blood values passes from a rapid into a slower phase.

ADRENALINE—HYPOGLYCEMIA

16 i.u. insulin administered intravenously to a grown person will in the course of 30 minutes give a characteristic clinical picture, known under the name of hypoglycemia. The hypoglycemic condition starts with subjective tremor and a beating of the heart. Thereafter strong sweat, numbness, and somnolence will develop in rapid succession. If the blood sugar declines further a condition of semiconsciousness may set in as well as convulsions. The hypoglycemia is accompanied by a gastric hypersecretion. It is a vagus conditioned secretion. *Cannon and his co-workers* (5) have examined the pathogenesis of the

hypoglycemic symptoms. They draw attention to the fact, that the hypoglycemic symptoms have essential features in common with the symptoms caused by adrenaline. In the first line there is heart beating owing to the accelerated action of the heart. From this they conclude, that the organism reacts to hypoglycemia with an overproduction of adrenaline from the suprarenal glands over the splanchnic nerve as efferent nerve. The production of adrenaline is the alarm reaction to the falling blood sugar, as adrenaline has a hyperglycemic effect. Today it is called a stress reaction. *Cannon* and his group used cats as experimental animals. After splanchnic section they became more sensitive to insulin, as all of them under the administration of insulin showed such a fall in blood sugar that they suffered convulsions. At the same time the workers showed, that the animals after splanchnicectomy did not react to hypoglycemia with increased acceleration at the pulse rate. They considered this as a sign of failing production of adrenaline after splanchnicectomy.

Haussay and his co-workers (23, 24) have by experiments on two animals, whose blood circulation they crossed, confirmed the theories of *Cannon* and his associates. They further showed that the secretion of adrenaline from the suprarenal glands started when the blood sugar reached to between 60 and 50 mg. per cent.

Not until recently did the investigators succeed in giving a direct proof that hypoglycemia causes increased production of adrenaline. With improved methods to show the presence of adrenaline *v. Euler* and *Luft* (44) in 1952 demonstrated that administration of insulin increases the secretion of adrenaline in the urine, and *Hökfelt* (25) later showed, that the suprarenal glands after large doses of insulin are emptied of adrenaline, which seems to indicate that the adrenaline secreted into the urine originates in the suprarenal medulla.

Owing to the difficulties in showing the presence of adrenaline in the blood (*A. Lund* (28)), it has not yet been possible to prove directly that the quantity of adrenaline in the bloodstream is increased under insulin hypoglycemia, but *Weil-Malherbe* and *Bone* (47) have recently worked out a method that should make such investigations possible.

In hyperglycemia the quantity of secreted adrenaline into the urine is conversely falling, (*Dunér* (10)) which shows that adrenaline is also active in the regulation of the blood sugar in downward direction.

ADRENALINE--SPLANCHNIC NERVE

In 1899 *Dreyer* (9) showed that stimulation of the splanchnic nerve resulted in secretion of blood pressure stimulating substances from

the suprarenal glands. These investigations have later been confirmed by *Tournade* and *Chobral* (40, 41) by experiments on dogs with crossed blood circulation.

It has now been showed by *v. Euler* (45) and *Gaddum, Péart* and *Vogl* (19) by direct demonstration of the substances, that stimulation of the splanchnic nerve results in secretion of adrenaline and nor-adrenaline from the suprarenal glands.

It is possible by indirect stimulation to make the suprarenal medulla secrete adrenaline and noradrenaline in varying mixture proportions dependent on the nature of the stimulation (*v. Euler* and *Folkow* (43)). Stimulation of the posterior half of the hypothalamus results in secretion of adrenaline from the suprarenal medulla via the splanchnic nerves. By varying the place of stimulation adrenaline and noradrenaline may be obtained in mutually varying quantities (*Folkow* and *v. Euler*, 1954, (16)).

THE EFFECT OF ADRENALINE ON BLOOD SUGAR

By releasing adrenaline under hypoglycemia the organism aims at keeping the blood sugar value constant. In 1902 *Blum* (2) demonstrated that adrenaline had a hyperglycemic effect by mobilizing the glycogen in the liver. *Cori* and *Cori* (6) have demonstrated that adrenaline may mobilize muscle glycogen by converting it into lactic acid, which then again is converted into liver glycogen. The main source of adrenaline for formation of glucose is, however, still the liver glycogen (*B. A. Houssay* and *R. Gerschman* (23)).

ADRENALINE—HYPOTHALAMUS

The secretion of adrenaline under hypoglycemia is released via the hypothalamus (*v. Euler* and *Folkow* (43)). *Dunér* (10) has demonstrated that the hypothalamus is direct sensitive to glucose as he could show that the adrenaline secretion from the suprarenal glands declined when a glucose solution was injected into the hypothalamus. *Safford* and *Gellhorn* (32) have further shown, that the hypothalamic vasomotoric centre under hypoglycemia reacts with increased rise of the blood pressure under acapnea as a manifestation of hyperirritability increased secretion of adrenaline from the suprarenal glands.

The hyperglycemia which is caused by the notorious sugar puncture (*Cl. Bernard*) in the floor of the fourth ventricle at the level of calamus scriptorius is indeed also due to hypersecretion of adrenaline from the suprarenal glands via the splanchnic nerves (60). Even if the sugar

puncture is released over the floor of the fourth ventricle, it is most probable that the blood sugar regulation is directed from the hypothalamus, and that medulla oblongata is a centre of secondary importance. Temporary glucosuria is a frequent finding in acute traumatic brain lesions and in cerebral hemorrhage.

If the hypothalamus is an important centre of the blood sugar regulation it is to be expected that the hypoglycemia secretion of adrenaline will decline under narcosis with barbiturates. There do not seem to exist any investigations of this problem.

OTHER BLOOD SUGAR STABILISING FACTORS

Cannon and his co-workers (5) thought that the power of the experimental animals to counteract the insulin hypoglycemia was quite suspended after splanchnic section, but *Berg and Zucker* (1) have in experiments on cats shown that the power of regeneration is not lost, as the blood sugar spontaneously rises, though at a slower rate than when the splanchnic nerves are intact. *Brouha and his co-workers* (3) *Elienne Martin* (12) and *de Takats and Cuthbert* (8) have examined the sensitivity to insulin in dogs after splanchnic section and also found spontaneous regeneration of the blood sugar values. *Freeman, Smithwich and White* (18) were the first to show the increased sensitivity to insulin in man after splanchnic section. It is, however, considerably less pronounced than in dogs and cats. *De Takats* and others (7) maintain that the insulin sensitivity is increasing after splanchnic section on account of reduced secretion of adrenaline. They have published a single blood sugar curve in illustration. *Simeone and Vavondes* (34) find reduced sensitivity to insulin in man immediately after splanchnic section, but the blood sugar curve is however wider, which means that the blood sugar regeneration is slower, even if the fall in blood sugar is less than normal. They do not state how long a time after the splanchnicectomy the insulin tolerance is examined.

On examining patients one year after the operation *Simeone and Ramires* (35) find a higher sensitivity to insulin as regards the greater fall of the blood sugar as well as the slower regeneration.

The increased sensitivity to insulin caused by section of the splanchnic nerve has induced the investigators to make an attempt at influencing diabetes by way of splanchnic section. A great amount of literature has appeared dealing with this problem. As diabetes is not due to any disturbances in the adrenaline production of the organism, and as the diabetic dysregulation is not aggravated by normal function of the suprarenal medulla—quite the contrary—there does not seem

to be any rational indication for splanchnic section in diabetes. The function of the adrenal cortex presumably remains undisturbed by splanchnic section (see below).

If a small dosis of insulin is given intravenously (0.2 i.u. per kilo body weight) to any animal that is either normal or has undergone splanchnic section no manifest hypoglycemic symptoms will develop and the blod sugar curves will follow the usual course (*Schlossberg, Sawyer and Bixby* (33)). In both categories of animals there will develop a temporary moderate fall in the blood sugar values and the curves will look alike. If on the other hand a larger dosis of insulin is administered (0.5 i.u. per kilo body weight) the difference in mode of reaction will be distinct. The hypoglycemic symptoms will develop when the blood sugar drops to about 60 mg. per cent. and as demonstrated by *Cannon* (5) they will essentially be marked by a toxic secretion of adrenaline, that sets in when the blod sugar falls to an alarming extent.

Insulin tolerance of animals after splanchnic section and examinations of subclinical falls in the blood sugar values caused by small quantities of insulin seem to indicate that the organism, besides adrenaline, also has access to other sugar stabilising substances which only act more slowly and therefore not to the same degree are suited to meet a catastrophe as adrenaline. *Fraser, Albright and Smith* (17) have shown that the sensitivity to insulin is increased by adrenal cortex and pituitary insufficiency. Hypophysectomized animals' (*Houssay* animals) increased sensitivity to insulin is also well-known. Conversely the insulin tolerance is increased in tumors in the adrenal cortex, for instance in *Cushing's* syndrome, and in hyperplasia in the adrenal cortex, as well as in certain forms of hyperfunction of the pituitary. The increased insulin resistance which *Simeone* and *Vavoudes* found immediately after splanchnic section is no doubt due to hyperfunction of the adrenal cortex as a consequence of the operation. Adrenal cortex hormones, or rather the fraction of the adrenal cortex hormones called the glucocorticoids, that chemically are oxycorticosterones, react diabetogenically, i.e. they counteract the insulin activity and increase the blood sugar. The glucocorticoids inhibit the oxidation of glucose by inhibiting the formation of hexosephosphate. Besides they act destructively on proteins and transform amino-acids into glucose, (*Harris* and *Harris* (22)).

Under insulin hypoglycemia with clinical hypoglycemic symptoms conditions round the formation of glucocorticoids are complicated as the adrenal glands secrete great quantities of adrenaline that stimulate the formation of ACTH (*Long* 27).

Thorn's test of the function of the adrenal cortex is based on the practical exploitation of this condition.

It is, however, of decisive importance to know whether hypoglycemia directly stimulates the production of ACTH, or whether the ACTH formation under hypoglycemia exclusively is due to the secretion of adrenaline. It seems most natural to assume that the blood sugar stabilising power of the organism after splanchnic section consists of glucocorticoids, even if the hypoglycemic adrenaline production has stopped. If the glucocorticoids alone shall keep the blood sugar constant it must be supposed that they are formed in greater quantities after splanchnic section than before. There are no direct investigations of the secretion of adrenal cortex hormones under the insulin tolerance before and after splanchnicectomy. The alterations in the gastric secretion under hypoglycemia after splanchnic section are, however, identical with the effect of ACTH on the gastric secretion. This seems to indicate that the ACTH production under hypoglycemia is higher after than before splanchnic section.

Splanchnicectomy and ACTH have further the same aggravating influence on the function of the adrenal cortex. The adrenal cortex is only sparingly innervated and *Michie* and *Clayton* (48) found in conformity with this that splanchnicectomy did not change the secretion of 17-ketosteroids. *Vogt* (50) has also shown that splanchnicectomy does not influence the secretion of the hormones of the adrenal cortex in normal conditions. Further, that the splanchnic stimulation does not result in the production of cortex hormones, provided that a simultaneous adrenaline secretion is avoided. The function of the adrenal cortex thus seems independent of the splanchnic innervation, as it is exclusively humorally determined by the pituitary ACTH production. Attention must, however, be drawn to the fact that *Okinaka* and *associates* (49) have demonstrated that splanchnic stimulation increases the secretion of desoxycorticoids.

ACTH—GASTRIC SECRETION

It is a well-known clinical experience that ACTH aggravates existing peptic ulcer, and for that very reason peptic ulcer becomes one of the contraindications for the administration of ACTH.

In conformity with this *Gray and his associates* (21) have found that ACTH increases acid secretion and pepsin secretion, though not the quantities of the gastric secretions.

Under the administration of ACTH the secretion of uropepsin in-

creases. *Janowitz and Hollander* (53) have shown that the secretion of uropepsin is increased in peptic ulcer. *Kirsner and his associates* (51) and *Zubiran and his associates* (52) have found increased gastric secretion after administration of ACTH. It is surprising that *Ferster and his associates* (54) have found that ACTH administered together with vitamin-C decreases the quantity of gastric secretion caused by histamine. It is possible that it is only the oxycorticoids that increase the gastric secretion as *Lahiri* (56) has found that the desoxycorticoids reduce the quantity of the secretion and the amount of total chlorides in the gastric secretion. The question of ACTH's influence on the gastric secretion thus is not quite cleared up. And not least is it important as regards the question of ACTH's relation to peptic ulcer.

Porter and his associates (57) have shown that stimulation of the posterior part of hypothalamus causes a tardive gastric secretion, that is hormonally regulated and dependent on continued function of the adrenal cortex, i.e. an ACTH conditioned gastric secretion. The secretion is apparently released from the same region from which *Folkow and v. Euler* (16) have been able to release secretion of adrenaline from over the adrenal medulla via the splanchnic nerves. It is presumably from the same region in hypothalamus that the adrenaline secretion is released under hypoglycemia. It is not a question of an ACTH production and gastric secretion released with adrenaline as a connecting link, as the gastric secretion and with that the production of ACTH is liberated when the medulla has been severed in the cervical region and thus excludes the adrenaline secretion that from hypothalamus is liberated over the splanchnic nerves. *Porter and his associates* have further shown that under insulin hypoglycemia and vagotomy gastric secretion is obtained that completely corresponds to that of the hypothalamus. As far as can be seen the last mentioned examinations have not been made on denervated suprarenal glands by medullectomy in the cervical region, so that the possibility cannot be excluded that the tardive hypoglycemic hypersecretion in the stomach is an adrenaline conditioned secretion provoked by ACTH, and not a primary ACTH secretion, all seems, however, to indicate that under insulin hypoglycemia as a primary consequence of the effect of the hypoglycemia on hypothalamus increased quantities of adrenal cortex hormones are formed.

In this relation it may be stated that *Grimson and his associates* (55) have found that insulin hypoglycemia in vagotomized patients causes a tardive gastric secretion. They explain it by incomplete vagotomy, but it is rather a question of a tardive ACTH conditioned secretion.

OWN INVESTIGATIONS

While engaged on examinations of the gastric secretion in patients under insulin hypoglycemia before and after splanchnic section undertaken in cases of hypertension it was noticed that the patients were more influenced by the hypoglycemic condition after splanchnicectomy. They were more drowsy and often more sweating. Several of them were semiconscious, and when a patient (no. 41) had an epileptic seizure under the postoperative insulin hypoglycemia it gave rise to a series of examinations of sensitivity in patients to insulin before and after splanchnicectomy.

In all 50 series of correlated pre- and postoperative insulin tolerance tests were carried out. Of these 33 were subjected to clinical examinations with a view to hypoglycemic symptoms. Exclusively objective hypoglycemic symptoms have been registered because the patients at some time or other were so far away that it was difficult to get information without interfering with the other examinations. It has been noted how strong the sweating has been; changes in sensorium have been observed and the following graded descriptions applied, somnolence, semiconsciousness, and epileptic fits accompanied by unconsciousness.

The results of the clinical examination appear from Fig. 1. 26 of the 33 patients showed distinct signs of stronger postoperative hypoglycemic symptoms, and in none of the patients were the hypoglycemic symptoms less pronounced postoperatively. The aggravation of the hypoglycemic condition did not only consist in intensified symptoms, but other symptoms were added which can be construed only as a sign of a more pronounced hypoglycemia. While only a single patient was preoperatively semiconscious, 16 were semiconscious after the operation. Further, two had epileptic fits accompanied by unconsciousness. The graph only registers changes in symptomatology and in intensity, but not in duration. Most characteristic for the postoperative hypoglycemic condition was, however, that it lasted considerably longer than the preoperative hypoglycemia. Generally the hypoglycemic symptoms had not disappeared at the conclusion of the examinations, when the patients were still weak and tired. 3 patients were still somnolent, so that it was necessary to give them glucose intravenously as it was impossible to make them drink. Even if the effect of glucose intravenously administered in case of hypoglycemia is well-known it is nevertheless quite a striking experience to see how quickly and completely its effect was in these patients.

As control five patients were examined 7-10 days after an operation for herniated disc. In clear contradistinction to the patients after

Fig. 1.

Hypoglycemic symptoms under insulin hypoglycemia (16 units insulin intravenously) before and after splachnicectomy.

No	Preoperatively			Postoperatively			Aggra- vated	Unal- tered	Im- proved
	Sweat	Somno- lence	Semicon- sciousness	Sweat	Somno- lence	Semicon- sciousness			
10	+	+	-	+	+	-	+		
15	+	-	-	+	+	-	+		
16	+	-	-	+	+	-	+		
18	+	+	-	+	+	-	+		
19	+	+	-	+	+	-	+		
21	+	+	-	+	+	-	+		
23	+	-	-	+	+	-	+		
24	+	-	-	+	+	-	+		
25	+	-	-	+	+	-	+		
26	+	+	-	+	+	-	+		
27	+	+	-	+	+	-	+		
28	+	-	-	+	+	-	+		
30	+	+	-	+	+	-	+		
31	+	+	-	+	+	-	+		
39	+	-	-	+	+	-	+		
41	+	-	-	+	+	-	+	(convulsions)	
43	+	-	-	+	+	-	+		
44	+	+	+	+	+	-	+		
49	++	-	-	+	+	-	+		
50	+	-	-	+	+	-	+		
52	+	+	-	+	+	-	+		
53	+	-	-	+	+	-	+		
58	+	+	-	+	+	-	+		
59	++	-	-	+	+	-	+		
60	+	+	-	++	+	-	+		
61	-	+	-	+	+	-	+		
62	+	+	-	+	+	-	+		
63	+	+	-	+	+	+	+		
65	+	-	-	+	+	+	+	(convulsions)	
68	+	+	-	+	+	+	+		
69	+	+	-	+	+	+	+		
86	+	-	-	+	+	+	+		
87	+	+	-	+	+	-	+		

Insulin Tolerance as control of 5 patients operated on for herniated disc.

88	+	+	-	+	-	-
89	+	-	-	+	+	-
90	+	+	-	+	+	-
91	+	+	-	+	+	-
92	+	+	-	+	+	-

splanchnicectomy three of the former was unaltered and two were less seriously influenced. It is, as already stated, probable that postoperative adrenal cortex hyperfunction may result in increased insulin resistance immediately after an operation. (*Franksson et al.* (58)).

Insulin tolerance curves have further been examined in the case of ten patients before and after splanchnicectomy. Simultaneously with the drawing of blood for blood sugar determination the pulse was taken so that it became possible to draw up curves of correlated values of blood sugar and pulse rate.

Fig. 2.

Variations in blood sugar level during insulin tolerance test before and after splanchnicectomy.

	0	10	20	25	30	35	40	45	50	55	60	65	70	min.
Pt. no. 10 preop.:	120			70	60	56	50		60		70		76	„
postop.:	94				51		48		48		56		64	„
Pt. no. 16 preop.:	96				54		45		53		66		80	„
postop.:	94				51		48		48		56		64	„
Pt. no. 18 preop.:	104	91	79		64		48		64		80		88	„
postop.:	92		63		55		47		50		62		70	„
Pt. no. 19 preop.:	100				53		60		72		80		82	„
postop.:	110				60		54		54		62		74	„
Pt. no. 20 preop.:	95	90			46		66		74		85			„
postop.:	88	80			45		45		64		75			„
Pt. no. 21 preop.:	90				45		60		58		80			„
postop.:	90				45		40		53		62			„
Pt. no. 23 preop.:			60		44	48	52	60	66		75			„
Pt. no. 48 preop.:	110			55	45	42	40	45	50		70	78		„
postop.:			56		42	40	40	38	45					„
postop.:	86			60	58	34	34		38		42	48		„
Pt. no. 60 preop.:	120			95	70	52	55	70	80		89			„
postop.:	135			110	55	35	50	66	77		80			„
Pt. no. 61 preop.:	135			100	79	68	68	85	89	97	99			„
postop.:	128			83	52	63	59	57	52		79	88	89	„

Fig. 2 shows the correlated value of the blood sugar before and after splanchnicectomy. Fig. 3 shows a typical insulin tolerance curve pre- and postoperatively with corresponding pulse curves.

The preoperative blood sugar curve shows an initial fall. Not until the blood sugar declines to about 60 mg. per cent. an increase in the pulse rate is observed, which is felt by the patient as beating of the heart. The increased pulse rate is according to *Cannon and his associates* a sign that the secretion of adrenaline sets in. Shortly afterwards the fall in the blood sugar stops, as the curve reaches a down-

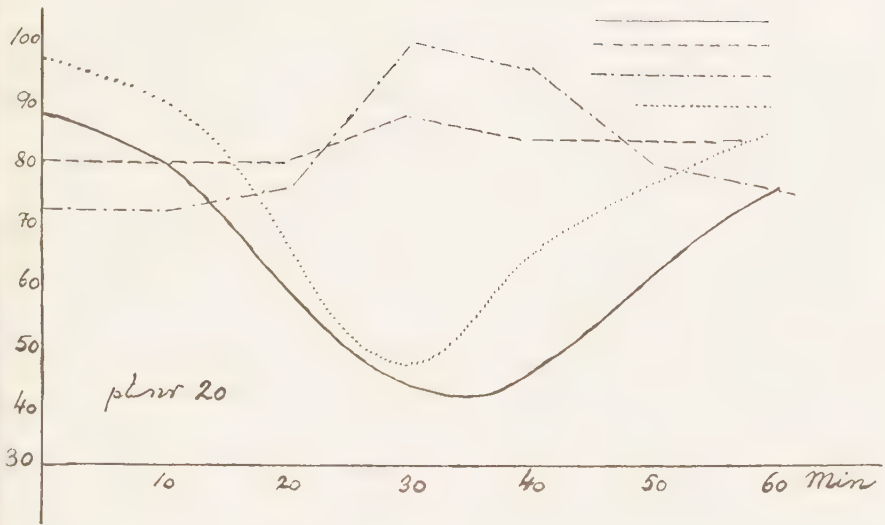


Fig. 3.

ward convex minimum. The blood sugar values generally decrease to between 40 and 50 mg. per cent, but only for a brief period are they lower than 70 mg. per cent, as the blood sugar curve rises steeply until this value is reached. In this place the "bend" observed by Brühl becomes distinct, and simultaneously the pulse rate once more declines (4). The bend in the curve is due to the fact that the blood sugar regeneration changes from a quicker to a slower course. The secretion of adrenaline is responsible for the rapid regeneration of blood sugar, and the bend in the curve is thus a sign that the secretion of adrenaline has stopped. Adrenaline has a rapid and very pronounced hyperglycemic influence, but it stops as soon as the secretion stops as adrenaline very quickly is destroyed in the organism. Thus adrenaline also in the fight against hypoglycemia constitutes an excellent weapon in any catastrophe.

After the bend in the ascending branch of the blood sugar curve a slight temporary decline may appear in the blood sugar values, otherwise the latter will increase smoothly at a slower rate to normal fasting values. There can be no doubt that other blood sugar stimulating forces carry on the effect of the adrenaline. As stated it is tempting to assume that these secondary blood sugar stimulating factors consist of hormones of the adrenal cortex.

After *splanchnicectomy* an initial fall in the blood sugar values occurs in principle in the same way as before *splanchnicectomy*. The fall is generally deeper, though not essentially so, nor is it of a characteristic nature. The fall in the blood sugar values is to some extent

Fig. 4.

Puls rate during insulin tolerance test before and after splanchnicectomy.

	0	10	20	30	40	50	60	70	min.
Pt. no. 10	68	68	68	96	104	100	80	72	„ preoperatively
	76	76	80	84	84	84	80	76	„ postoperatively
Pt. no. 16	64	64	64	96	88	92	80	76	„ postoperatively
	72	72	72	80	84	80	80	80	„ postoperatively
Pt. no. 18	72	72	72	100	104	80	76	76	„ preoperatively
	80	76	80	88	88	80	80	80	„ postoperatively
Pt. no. 19	76	76	76	104	100	88	80	80	„ preoperatively
	76	76	76	96	96	80	80	80	„ postoperatively
Pt. no. 20	72	72	76	100	96	80	76		„ preoperatively
	80	80	80	88	84	84	84		„ postoperatively

dependent on the time, that is allowed to elapse after the operation before the insulin tolerance test is undertaken. *Simeone* and *Vavoudes* (34) found that the blood sugar immediately after the operation did not decline as much as before the operation. In my ten patients, who have been examined 10–12 days after the operation, the postoperative blood sugar curve is in all the cases lower than the preoperative, though the difference is often slight only.

The most characteristic feature in the postoperative blood sugar curve is that it is wider because the blood sugar regeneration is slower. Simultaneously it is noted that the increase in the pulse rate is less pronounced than preoperatively, though not abolished as *Cannon* (5) found in cats. This tends to show that splanchnicectomy in man does not lead to as complete a denervation of the adrenals as in the animal experiments on dogs and cats. On the basis of the given anatomical conditions *Peel's* operation must at any rate be an incomplete denervation of the adrenals. There is, however, no striking difference in the blood sugar curves after *Peel's* and after *Smithwick* and *White's* operations. The lastmentioned operations include a resection of the first and second lumbar ganglia over which the preganglionic fibres to the adrenals should chiefly pass. If this is the case they do not seem to have been of any essential importance for the secretion of adrenaline in the adrenal glands under hypoglycemia.

As a reason for persistent secretion of adrenaline after splanchnic section in man the existence of possibly aberrant chroma-fine tissue may be suggested. It is found in greater quantities in man than in dogs and cats.

By a comparison of the clinical course of the hypoglycemic symptoms and the blood sugar curves they are seen to be completely cor-

responding. A direct examination of the secretion of adrenaline after splanchnicectomy would be of great theoretical as well as practical interest. In the first line the fall in the secretion of adrenaline under hypoglycemia will be a direct sign of the effectivity of the splanchnicectomy which would be of particular value in follow-up examinations of patients after splanchnic operations. The insulin tolerance curves would confirm the fact, but the practical difficulties in drawing up blood sugar curves are greater than those involved in the determination of secretion of adrenaline in the urine, and the blood sugar curves are more difficult to interpret.

Splanchnicectomy does not directly influence the formation of adrenal cortex hormones, but indirectly through a reduction of the adrenaline secretion there is a possibility that splanchnicectomy may influence the formation of adrenal cortex hormones. The importance of the latter for the pathogenesis of hypertension sets one thinking. At the present time it seems, however, difficult to form a theory in which changes in the production of adrenal cortex hormones in connection with splanchnicectomy may give a therapeutically favourable result to splanchnic section.

It is possible that the most important effect of splanchnicectomy in hypertension alone is to be found in a reduction of the power of the organism to secrete adrenaline under stress. *Smithwick and his co-operators* (59) have thus shown that patients after splanchnic section react by a smaller increase in blood pressure on "cold pressor tests" than before the operation. Clinical experiences with splanchnic section in hypertension also tend to show that rather a stabilising of the blood pressure than a depression of same is achieved. More thorough examinations of the function of the adrenal cortex after splanchnicectomy may possibly contribute towards the application of splanchnic section in hypertension, as also blood sugar curves and pulse curves under insulin tolerance tests and examinations of secretion of adrenaline in the urine under insulin hypoglycemia may be applied as valuable tests of the effectivity of splanchnicectomy.

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D'UN SYNDROME CEREBELLEUX PROGRESSIF A LA PHASE TARDIVE DE L'EPILEPSIE ESSENTIELLE¹

Par

LUDO VAN BOGAERT et GASTON COLLE

Le problème des déterminations cérébelleuses chez les épileptiques peut se poser sur deux plans: celui de la clinique et celui de l'histopathologie nerveuse.

Nous aborderons dans ce travail l'un et l'autre.

C'est Spielmeyer (1924) qui, le premier, a montré que dans les épilepsies les plus diverses on trouve des altérations récentes et anciennes dans les cornes d'Ammon et le cervelet. Les lésions de la corne d'Ammon étaient connues avant ses travaux mais pas celles du cervelet. Il les séparait des altérations générales du névraxe qu'on trouve chez beaucoup d'épileptiques qui ont eu de nombreux accès et qu'on mettait en relation avec le gonflement cérébral de Reichardt.

Ces lésions décrites par Spielmeyer dans le cervelet consistaient surtout en armatures gliales prenant la place des éléments de Purkinjé détruits et de leurs axones (Sagel, 1921) et en une altération dégénérative des cellules de Purkinjé consistant en une disparition des corps de Nissl, une pâleur du protoplasme, une modification du noyau et des nucléoles consistant en une perte de leur colorabilité et une modification de leur chromatine (modification homogénéisante de Spielmeyer, 1922).

Ces altérations qu'il interprète d'abord comme des altérations systématisées dégénératives, il les attribue plus tard à un désordre ischémique local. La preuve du bien fondé de ce mécanisme fut apportée par Uchimura pour les lésions équivalentes de la corne d'Ammon.

L'addition et l'accumulation de ces armatures gliales déterminées par les troubles vasculaires de paroxysmes comitiaux peuvent aboutir à des nécroses de la moléculaire, à des éclaircissements « en taches » (Spielmeyer, 1926).

¹ Travail du Laboratoire de Neuropathologie de l'Institut Bunge (Berchem-Anvers) et de l'Institut Psychiatrique de Beernem.

C'est à l'instigation de Spielmeyer que Liebers les a soumis à une nouvelle étude en 1928, basée sur le matériel même du laboratoire de Munich. Les neuf cas de ce travail ne comportent que quatre cas avec des altérations cérébelleuses nettes et l'histoire clinique de ces épileptiques jeunes et d'âge moyen ne présentait rien de particulier.

Dans son troisième cas (Töpel), concernant un jeune épileptique de 20 ans avec démence, le processus est étendu à un grand nombre de lamelles d'un axe et dans ce cas la raréfaction des grains est plus importante, certains grains présentant les altérations que Schob a décrites dans les atrophies (arrondissement du corps cellulaire, hyperchromatose de la paroi, perte du nucléole etc. . .) Dans ce même cas il y a une perte importante en cellules de Purkinjé, une dissociation de cette couche avec la couche des grains, une gliose atrophique de la moléculaire et même dans les préparations par la méthode de Bielschowsky on trouve des aspects qu'on peut observer dans les atrophies.

Son quatrième cas est encore plus accentué: le processus est surtout hémisphérique et non vermien.

Liebers montre dans ce travail que par sommation de ces atrophies et scléroses insulaires on arrive à des atrophies et scléroses de lamelles entières accompagnées d'une importante sclérose axiale.

Ce sera Scherer (1931) qui reprendra ce même travail. Il montre que le développement en surface de cette atrophie lamellaire est assez variable et qu'il n'y a pas de règles à ce sujet: l'atteinte du dôme lamellaire est aussi fréquente dans l'épilepsie que l'atteinte des sillons. Une perte de la couche des grains sous forme de taches n'a été observée par lui qu'une seule fois sur 27 épileptiques – alors qu'un éclaircissement diffus est trouvé souvent dans cette affection et traduirait pour lui suivant l'école de Spielmeyer un spasme vasculaire étendu à de grands territoires cérébraux. Cet éclaircissement diffus, ajoute Scherer, peut « se présenter rarement d'une manière isolée, le plus souvent combinée à une autre affection, à une perte étendue des Purkinjé avec prolifération débutante de la couche de Bergmann c.à.d. à un début d'atrophie lamellaire ».

Scherer a noté aussi ce fait qui est important en ce qui concerne notre observation, qu'à distance des zones de sclérose lamellaire on peut observer des processus atrophiques rappelant ou même reproduisant exactement ce qu'on observe dans les abiotrophies.

De fait, il existe dans la littérature de rares cas où la coalescence de ces secteurs d'atrophie lamellaire aboutit à une grave sclérose de l'organe tout entier.

Nous n'avons pas fait la littérature détaillée de ces cas et nous nous contenterons de rappeler ici les observations de Hassin (1934) publiées

sous le nom de « sclérose atrophique du cervelet ». Le vermis était épargné: le processus atrophique se limitait à la partie supérieure et antérieure des hémisphères cérébelleux.

Le premier cas de cet auteur est une jeune femme de 27 ans avec un syndrome de soi-disant hyperthyroïdie avec instabilité, asthénie et agitation. Elle succomba à un état toxi-infectieux grave, attribué à une leucémie mais ne présentant *aucun signe cérébelleux*. A l'autopsie le cervelet présentait à la face supérieure, au niveau du lobe semilunaire et quadrilatère des zones de sclérose lamellaire avec des altérations importantes.

Dans le second cas, une jeune femme de 32 ans, cataloguée hémiphrénie, était devenue irritable, hypersexuelle et fit une crise épileptique avec violence et tendances destructrices. Elle présentait un délire de persécution mais *aucun signe cérébelleux*.

Les lésions étaient analogues mais bilatérales. Le processus se limitait par îlots à certaines lamelles cérébelleuses, intéressant à la fois les éléments de Purkinjé et les grains.

A ce propos Hassin rappelle que des lésions analogues ont été décrites dans les thromboses artérielles, les processus inflammatoires, une méningite chronique ou même dans des processus compressifs chroniques comme la maladie de Paget (Grünthal) ou un angiome racémeux (Lehoczky). Ce rapprochement n'apporte rien de neuf: il est plutôt de nature à apporter de la confusion car il est évident que ces thromboses cérébelleuses ou ces atrophies par compression n'ont rien à faire avec une atrophie par sclérose lamellaire.

Ces analogies en fait superficielles ont cependant conduit les auteurs à se demander si le cervelet n'avait pas les mêmes formes de réaction aux influences nocives dans les processus aigus et chroniques. On peut, avec Zülch, objecter aussitôt à cette tendance uniciste que l'atteinte aiguë des cellules de Purkinjé n'est pas l'indice d'une altération systématisée.

Les observations de « sclérose atrophique » de Hassin, les nécroses corticales des déterminations vasculaires ou inflammatoires ne se présentent pas cliniquement comme des syndromes cérébelleux progressifs.

Une exception est celle des syndromes compressifs progressifs par exemple de la maladie de Paget où nous avons déjà observé nous mêmes un syndrome cérébelleux compliqué d'altérations des nerfs crâniens.

Mais un syndrome cérébelleux progressif est, à notre connaissance, exceptionnellement souligné dans les phases tardives de l'épilepsie simple. Nos quelques recherches dans la littérature à ce sujet ont même été négatives.

L'observation suivante est un cas de cet ordre et nous avons pensé à le rapporter parce qu'une vérification fut obtenue qui confirma la réalité du substratum de l'affection.

Lucien Mill (1921-1950).

Antécédents personnels: Ce malade souffre depuis l'âge de six ans de crises d'épilepsie. Pas de maladies particulières depuis mais abus manifeste de tabac. Il travaillait dans une brasserie jusqu'au moment de son entrée mais il ne semble pas y avoir eu d'excès alcooliques. Il fut admis à l'Institut Psychiatrique de Beernem à l'âge de 24 ans.

Antécédents héréditaires: Rien de spécial. Enfant unique.

Examen: A l'entrée de malade était obnubilé, très ralenti dans ses fonctions psychiques et présentait de nombreuses absences. Il se redressait parfois brusquement, devenait pâle et faisait quelques gestes inattendus, pseudobulbaires, rappelant tantôt une décharge jacksonienne, mais le plus souvent stéréotypés et apparentés aux gestes obsessionnels. Il présentait une ou deux fois par jour des absences ou équivalents psychomoteurs. Dans l'interrogatoire il se contredit fréquemment.

L'examen neurologique à ce moment ne semble avoir présenté aucune particularité.

Evolution: Au point de vue psychiatrique, il continua à présenter un délire hallucinatoire. Il passait des heures entières assis à l'entrée du jardin, paisiblement, attendant « Suzanne » qui viendrait pour l'épouser.

Ses accès épileptiques n'ont pu être contrôlés malgré 0,30 de Solantyl et 0,10 de Luminal par 24 h. Il avait cinq à six accès importants par jour et un grand nombre d'absences. L'état général demeura bon jusqu'en 1950. Il présentait au point de vue neurologique une abolition des réflexes tendineux, achilléens et patellaires aux deux membres inférieurs. Pas de signe de Babinski. La parole s'accompagne d'un tremblement et elle est relativement sourde.

En Mai 1950 il fait une chute sur le dos et depuis cette époque son état général est moins bon.

Lors d'un examen général et neurologique le 2.X.1950 on note son teint foncé, presque bronzé, une légère desquamation de la peau du front et des joues.

La parole est devenue incompréhensible et sourde. Il regarde continuellement ses mains qui sont animées de petits mouvements reptatoires irréguliers, variables, rappelant plutôt la chorée mineure que l'athétose. Les doigts sont hippocratiques. Pas de mouvements involontaires au niveau de la face. Pas de secousses myocloniques.

Au point de vue somatique: léger subictère conjonctival, tachycardie (28×4) avec hypotension ($11,5/7$), acné thoracique, rien aux poumons. Foie et rate rien de particulier. Pas de ganglions. Glossite et stomatite très douloureuses.

Au point de vue psychique: le malade est très obnubilé. Il répond cependant aux ordres simples mais pour le reste il est impossible d'entrer en contact avec lui. Il réagit aux excitations douloureuses.

Il présente une dysmétrie nette aux quatre membres avec un tremblement intentionnel typique. La parole est sourde et légèrement scandée.

La marche est ataxique. Elle est impossible s'il n'est pas soutenu.

Les jambes sont amaigries. La musculature est dans son ensemble très peu

fournie sans qu'on puisse parler d'une véritable atrophie. Les réflexes tendineux des membres supérieurs sont faibles. Ceux des membres inférieurs sont abolis.

Les réflexes cutanés plantaires sont en flexion, les abdominaux absents. Du côté des nerfs crâniens: rien de particulier. Les réflexes pupillaires à la lumière sont lents.

Le fond d'œil est normal.

Dans les trois dernières semaines de la vie, l'ataxie devient de plus en plus marquée, il est aussi plus apathique, ne manifeste aucune douleur, la peau devient plus bronzée, continue à desquamer, la musculature s'amenuise encore. La voix devient plus sourde, la parole moins intelligible.

Il meurt le 26.X.1950.

L'histoire clinique peut se résumer comme suit: épilepsie essentielle depuis l'âge de six ans. Démence ayant apparu insidieusement vers la vingtième année et ayant nécessité un internement à 24 ans. Les deux dernières années de la vie apparition d'un tremblement généralisé avec de petits mouvements involontaires des mains, une ataxie cérébelleuse avec tremblement intentionnel et décomposition des mouvements. Etat général et psychique de plus en plus mauvais.

ETUDE HISTOPATHOLOGIQUE

Technique (I. B. 6/51): Celloidine, Woelcke-Heidenhain, crésylviolet.

A. Topographie des lésions.

De grandes coupes ont été pratiquées à travers la région frontale. Sur les préparations myéliniques on ne voit rien de particulier.

Sur les coupes cytologiques: en dehors d'une méningite fibreuse chronique, assez banale, l'architecture cellulaire est partout respectée. Il n'y a pas de gliose, les cellules sont dans toute l'étendue du cortex, particulièrement en ce qui concerne les cellules pyramidales moyennes, rétractées et présentent un aspect hyperchromique.

Dans l'axe blanc: rien de particulier.

Une coupe intéressant la région de l'hippocampe montre l'intégrité parfaite de la bande pyramidale ammonique. Le secteur fragile est entièrement respecté, de même que les structures avoisinantes de la circonvolution fusiforme.

Une grande coupe passant par les noyaux gris centraux montre l'intégrité de la couche optique, sauf au niveau du noyau ventro-latéral qui est légèrement éclairci. La formation réticulée paraît intacte. Le putamen a sa structure normale ainsi que l'avant-mur. Le pallidum est pauvre en cellules, mais ne présente pas de gliose manifeste. Le corps de Luys et les corpuscles mammillaires sont intacts. Dans les préparations myéliniques du même niveau on est frappé également de la pauvreté des systèmes myéliniques propres du pallidum, surtout au niveau de son segment externe, par contre, la couche optique a son aspect normal. La substance noire ne présente rien de particulier.

Sur une coupe myélinique vertico-transversale du cervelet on remarque déjà une certaine pâleur des lamelles de la face ventrale et en particulier de l'amygdale et du lobe semilunaire inférieur. Si l'on compare à ces coupes myéliniques les coupes cytologiques on voit immédiatement que là aussi les mêmes secteurs sont

beaucoup moins bien colorés. Il y correspond, à un plus gros agrandissement, des raréfactions sinon une disparition des cellules de Purkinjé et, par endroits, un éclaircissement de la couche des grains. En regardant minutieusement les lamelles de la face dorso-ventrale, on voit ce processus de raréfaction des cellules de Purkinjé s'ébaucher par lamelles. L'appauvrissement extrême qu'on voit à la face inférieure n'étant en quelque sorte que la forme extrême du même processus.

Les lamelles ventro-médianes du noyau dentelé montrent une gliose cellulaire et les vaisseaux du hile, une très discrète infiltration.

Sur les coupes du cervelet passant par le même niveau on voit que les circonvolutions atropiques et le noyau dentelé sont le siège d'une gliose discrète et diffuse. Il est impossible de mettre en évidence une telle gliose dans les noyaux gris centraux, par contre dans la moëlle cervicale haute (C1) il y a incontestablement une gliose fibrillaire du secteur correspondant au cordon de Goll.

Si nous résumons l'ensemble de ces *données de localisation*, en dehors d'une atrophie cérébelleuse prédominant sur la face ventrale de l'organe, de l'atteinte légère du noyau dentelé, de la raréfaction légère du pallidum il n'y a pas d'autres lésions.

B. Quant à la *structure histopathologique* du processus morbide il s'agit avant tout d'une coalescence de lésions de sclérose et d'atrophies lamellaires qui ne diffèrent en rien de ce qu'on voit dans les autres atrophies lamellaires connues.

Il vaut peut être la peine de revenir un instant sur la seule observation connue où une addition des lésions lamellaires a donné un tableau cérébelleux caractérisé, mais elle tombe en dehors de l'épilepsie.

C'est l'*observation princeps* d'André Thomas (1905), publiée sous le nom d'« atrophie lamellaire des cellules de Purkinjé ». Chez cette femme de 54 ans avait apparu à l'âge de 40 ans un syndrome cérébelleux progressif, caractérisé par de l'ataxie, du tremblement intentionnel et de l'hypotonie, au point qu'on avait pensé à une sclérose en plaques. Cette malade avait fait plusieurs infections, dont la syphilis, et buvait assez bien d'alcool. A l'autopsie le cervelet était normal mais à l'examen histologique, André Thomas décrit « des lésions indubitables essentiellement caractérisées par l'atrophie et la disparition d'un certain nombre de cellules de Purkinjé, auxquelles s'étaient substitués des amas de noyaux ou des réseaux névrogliques plus ou moins épais. Cette raréfaction des cellules de Purkinjé ne s'est pas faite d'une façon quelconque puisque certaines lames ou lamelles en étaient complètement dépossédées, alors que sur d'autres leur nombre paraissait normal ».

André Thomas ajoutait: « Il s'agit en quelque sorte d'une atrophie procédant lamelle par lamelle, d'une atrophie lamellaire. Sur ces



Fig. 1.

Une vue d'ensemble d'une coupe verticotransversale du cervelet montre un ensemble d'atrophies lamellaires de la partie médio-ventrale de l'hémisphère avec accentuation des lésions au niveau de la région médiane, ce processus étant rigoureusement symétrique (celloïdine - crésylviolet).

mêmes lamelles la couche moléculaire est plus riche en noyaux et en corpuscules amyloïdes. Les grains sont irréguliers, plus espacés, plus mélangés de noyaux névrogliques. Ces lésions sont indépendantes de toute altération méningée et vasculaire ».

Ce cas est un peu plus complexe que le nôtre à cause de l'existence de lésions dans la corne antérieure qu'André Thomas homologue à celles de l'écorce cérébelleuse: lésions unilatérales ou tout au moins prépondérance unilatérale et limitées à la région lombaire.

Dans les atrophies lamellaires ou cérébelleuses d'origine exogène on ne voit faire aucune part à l'épilepsie.

Les scléroses lamellaires sont dans des cas comme celui-ci – au même titre que les éclaircissements cellulaires de la couche optique (noyau dorso-médian surtout) – la signature de la composante vasculaire du processus comitial. Le secteur de Sommer était néanmoins intact.

Un cas comme le nôtre, dont la localisation préférentielle est à l'opposé des localisations dorso-caudales de l'abiotrophie et de la sénescence, complète la chaîne qui relie l'atrophie lamellaire en secteur à des processus plus généraux, comme ceux de Hassin.

Il se rapproche par bien des points des atrophies cérébelleuses de l'artériosclérose qui peuvent être familiales (Mutrux, 1951), qui se présentent également comme une addition des atrophies lamellaires multiples mais où l'association d'un état lacunaire ou criblé du strié ajoute une signature non récusable.

L'intérêt d'une telle observation est de montrer qu'à la longue, les déterminations vasculaires fonctionnelles de la crise épileptique peuvent, additivement, réaliser un syndrome clinique permanent et explicite. Ce syndrome de sclérose cérébelleuse de l'épilepsie a sa place à côté du syndrome de sclérose cérébelleuse des affections vasculaires cérébrales.

Nous avons pensé qu'une telle observation ne déparerait pas la gerbe d'hommages que la Neurologie apporte aujourd'hui au Docteur Knud Krabbe dont l'œuvre neurologique si fouillée et si ample touche à la fois aux domaines de la sémiologie nerveuse et de la neuropathologie. Qu'il veuille trouver ici l'expression d'une fidèle et vieille amitié.

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NEUROSECRETION IN MAN UNDER STRAIN

1. A Survey and a Contribution

(Aided by a grant from King Christian X's Foundation and the
P. Carl Petersen Foundation)

By

FREDERIK BOM

INTRODUCTION

On a temporary investigation of the hypothalamic changes in patients who died of delirium acutum, the author often found (1953), besides an intense chromophobia of the ganglion cells, a marked increase of the physiological vacuolization in the supraoptic and paraventricular nuclei.

As a description of the clinic and the pathogenesis of delirium acutum are outside the scope of the present publication, the reader, concerning these matters, is especially referred to the works of *Linggjærde* (1940, 1941, and 1954), who since 1940, consistently has used adaptation-physiological points of view regarding this syndrome, for which reason it is therefore necessary only to point out that patients with delirium acutum are exposed to a combination of serious psychic and somatic stress, and that the syndrome often ends fatally, as the highly excited patients perish in a shock-condition with circulatory insufficiency, hyperpyrexia, pulmonary complications, hypoxia, and dehydration. Considering this, it would seem justified to regard the neuro-histological changes mentioned as an expression of greatly increased activity of the ganglion cells concerned, and finally exhaustion of these.

¹ I am greatly indebted to *Professor O. Strange Petersen, The Institute of Social Research, University of Aarhus*, for aid and suggestions regarding the statistical evaluation of the material.

As is well-known, the vacuolization of the supraoptic and paraventricular ganglion cells is a physiological phenomenon relating to the neurosecretory processes in these cells.

One of the main purposes of the present work is, therefore, to establish a possible relation between the degree of this physiological vacuolization and the terminal stress to which the patients have been exposed. For this purpose the vacuolization of the nucleus supraopticus has been compared, respectively, in a group of patients having died after severe and protracted stress of the syndrome *delirium acutum* with a control-group consisting of patients having died suddenly (or rapidly) without such prolonged stress.

HISTORICAL REVIEW

The supraoptic ganglion cells: The ganglion cells of the nucleus supraopticus, and the magnocellular part of the nucleus paraventricularis are extremely characteristic large cells of an autonomic type with very ample, mostly marginally condensed Nissl material (cf. *Gagel*, 1928). They are exceedingly richly vascularized by means of a special capillary system (*Finley* 1940, *Craigie* 1940), and extremely resistant to disturbances of the circulation, resp. hypoxia (*Grenell & Kabat* 1947), all these things indicating the vital importance of the function of these nuclei.

The concept of neurosecretion: The observation of the above-mentioned characteristic traits, combined with the physiological existence of partly colloid-carrying vacuoles and/or colloid inclusions in the cell body, both in vertebrates and in numerous invertebrates was soon perceived by several investigators to be an indication of a secretory activity.

The neurosecretory phenomena were originally observed by *Speidel* (1919) and, independently, by *E. Scharrer* (1928), but it is undisputably the latter, coupled with *B. Scharrer* and later on *Bargmann* and co-operators, who is mainly responsible for the development of the neurosecretory theory. According to *Scharrer* (1954) "the concept of neurosecretion developed from the observation of nerve cells which also show the cytological characteristics of gland cells" and elsewhere he remarks that the neurosecretion actually represents an archaic form of endocrine secretion.

Critics of this theory have objected that it might be a question of fixation artefacts, products of degeneration, postmortem changes, etc., or that the colloid possibly originated in the pituitary gland, but *E. & B. Scharrer* (1940, 1945 and 1954) have decisively rejected this cri-

ticism, among other things by the examination of an extensive animal-material including demonstration of the colloid in supravital preparations. *Scharrer* (1940) pointed out that the neurosecretion does not originate in the pituitary gland by demonstrating a normal content of neurosecretion in toads, hypophysectomized long before, as well as the existence of neurosecretory phenomena in animals (invertebrates) without any pituitary gland. Thus the existence of a neurosecretion must be considered a reality.

Besides *E. & B. Scharrer* (1940, 1945, and 1954) numerous other investigators have, however, partly in co-operation with *E. Scharrer*, valuably contributed to the development of the neurosecretory theory, especially: *Scharrer & Gaupp* (1933), *Gaupp & Scharrer* (1935), *Gaupp* (1934 and 1935), *Roussy & Mosinger* (1934 and 1946), *Mosinger* (1949 and 1950), *Peters* (1935-36 and 1951), *Bargmann & Scharrer* (1951), and others.

Of late years here in Europe especially the Kieler school: *Bargmann* (1949 and 1954), *Bargmann & Hild* (1949), *Bargmann, Hild, Ortman & Schiebeler* (1950), *Ortman* (1951), *Hild* (1952), *Zeller & Hild* (1954), has extended the neurosecretory theory by extremely convincing combined neurohistological and physiological investigations. Also Scandinavian scientists, such as *Hillarp* (1949), *E. Hanström*, *Lundberg*, *E. Thomsen* and *M. Thomsen*, have contributed valuably, mostly from the zoological point of view.

From the investigations on animal-material by *Bargmann* and collaborators it would appear that, in all probability, the antidiuretic hormone originates in the hypothalamic nuclei from where, by means of the neurosecretory carrier-substance via the axons of the supraoptic-hypophyseal tract, it is transferred to the post-pituitary lobe, where it is stored up and later on released by the aid of a hypothalamic osmoregulatory mechanism which simultaneously activates the neurosecretion (cf. *Verney*, 1947). Thus neurosecretory granules have selectively been detected which follow the axons of the supraoptic-hypophyseal tract, and by cutting the pituitary stalk on frogs, *Hild* (1952) demonstrated that in a few days neurosecretory material accumulated in the proximal fragment. Furthermore *Hild* (1950 and 1952) and *Zeller & Hild* (1954) have pointed out that extracts of the neurosecretion from the supraoptic, and paraventricular area, injected into different mammals have the same physiological effects as the ordinary factory-preparations of the "posterior lobe hormones", and that there is a very close quantitative parallelism between the histologically (i.e. photometrically) determined neurosecretion and the hormone content physiologically estimated.

Formation of the neurosecretion: According to the investigators mentioned the neurosecretion is first developed within the area of the Nissl bodies, possibly at the expense of these, as the Nissl material decreases while the neurosecretion increases in quantity and finally may fill up the cell completely. At the same time vacuoles are formed (at any rate in numerous species of animals) which are mainly marginally arranged. These are at first small, but gradually increase in size and may finally give the cell a foam-like structure.

The vacuoles may either be more or less colloid-loaded, or empty. It still does not seem to have been established for certain whether the colloid is identical with the ultimate neurosecretion or represents an early stage of it, or finally, whether the vacuolar colloid—as suggested by *Peters* (1951)—possibly represents a metabolic product of the secretory cells. According to *Divry* (1934) and *Schiebler* (1950) the colloid is of a glyco-lipo-protein-like character.

The vacuoles: Regardless of the still unsettled points of view, concerning the relation between the vacuolar colloid and the ultimate neurosecretion, it appears, however, from the observations of the various investigators, that in the numerous species of animals (incl. homo) where vacuoles are found at all, they are intimately connected with the active phase of neurosecretion, and the vacuolization increases to the same extent as the secretory activity. Therefore it seems permissible to use the degree of vacuolization to form a rough quantitative estimate of the strain on the neurosecretory apparatus, resp. of the degree of the neurosecretory activity changes.

Naturally the ideal method ought to be a quantitative estimation of the ultimate neurosecretion, but as far as the hypothalamus is concerned, an exact photometric determination of the *Gomori*- (i.e. chrome-alum-hematoxylin-phloxine)-stained neurosecretion is unfortunately obstructed by the simultaneous co-staining of the Nissl material.

Over-strain of function: Under acute overloading of the antidiuretic function in rats by hypertonic NaCl-injections after a few hours *Hillarp* (1949) (on *Einarson*-stained slides) observed "a distinct chromatolytic reaction" in the supraoptic and paraventricular ganglion cells, i.e. disintegration and disappearance of the Nissl bodies without definite changes in the nuclei or nucleoli—(in the terminology of the *Einarson*-school one might as well prefer the word "chromophobia" to describe this sort of changes)—yet after 22 hours the cells were essentially restored.

Ortmann (1951-52) has—also on rats—performed similar, but more extensive experimental overstimulation of the antidiuretic system.

during which he noticed well-defined activity changes of the neurosecretory ganglion cells and by overstrain finally a genuine chromatolysis. These changes, however, occurred considerably more slowly than those observed by *Hillarp* (i.e. not until after 5-6 days). *Orlmann* ascribes this to the presence of a hormone depot in the posterior lobe, suggesting that the more rapidly appearing changes in *Hillarp's* experiments had no immediate relation to the neurosecretion, but were caused by the initial overstrain of the ganglion cells, accompanying increased innervation of the posterior lobe.

Regardless of these different opinions it should be emphasized that the above-mentioned rather slow, osmotically provoked activity changes of the neurosecretory ganglion cells, correspond very closely to the structural changes of autonomic ganglion cells produced in less than an hour by *Einarson & Lorentzen* (1946) through electric stimulation.

The neurosecretory stimulus: From the above-mentioned investigations, as well as the findings of *Verney* (1947), it would preliminarily appear that the most important neurosecretory stimulus is changes in the osmotic pressure of the arterial blood, i.e. dehydration and after that, emotional stress, which was proved by *Verney* to cause inhibition of the diuresis in dogs.

Neurosecretion in man: So far only a few investigators have dealt with the neurosecretion in man, to some extent probably because of the difficulty in obtaining real experimental conditions.

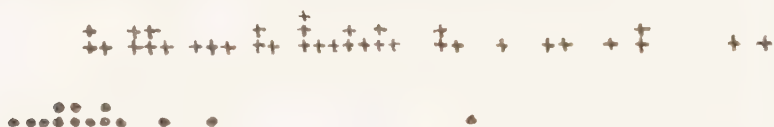
The neurosecretory phenomena in man were first described by *Scharrer & Gaupp* (1933) and later on especially dealt with in the works of *Gaupp* (1934, 1935), *Gaupp & Scharrer* (1935), *Dibry* (1934), *Roussy & Mosinger* (1934, 1946), *Peters* (1935-36, 1951) as well as *E. & B. Scharrer* (1940, 1945, 1954).

Both *Peters* (1935-36) and *E. & B. Scharrer* (1940) tried to establish a relation between the intensity of vacuolization (resp. the colloid content) in the neurosecretory ganglion cells, and the clinical symptoms, but in vain, possibly because more importance was attached to the clinical "main disease", existing in vivo, than to the terminal (preagonal) syndrome, resp. as to the character and intensity of the terminal stress, which among other things, owing to the violent strain on the fluid balance of the organism must probably be decisive of the neurosecretory state of activity found in the cells on the histological examination.

PERSONAL INVESTIGATIONS OF SUPRAOPTIC VACUOLIZATION

Method: The examinations were made on formalin-fixed frontal paraffin sections through the anterior hypothalamus and—with a very few exceptions stained by Einarson's progressive galloxyanine-chromealum method. The slides were usually examined at a magnification of 300 times (i.e. objective $\times 30$, ocular $\times 10$), and at least 200 (usually more) supraoptic ganglion cells from each of the brains dif-

5 10 15 20 25 30 35 40 45 50 55%
Total percentage of vacuolized cells:



Percentage of large-vacuolized cells:



5 10 15 20 25 30 35 40 45 50 55%

Fig. 1.

Dispersion of the material. The diagram shows the very pronounced and significant difference in the degree of vacuolization between the control group (.....) and the delirious brains (+++++).

ferential-counted by means of an ocular counting-chamber. Consequently all the percentages stated, of course, are only applicable to the magnification mentioned.

In a few brains (only 5,—marked with a * in the diagram) where the sections for some reason or other have not hit the supraoptic nucleus, the differential-count has, instead, been made on the morphologically and functionally analogous magnocellular part of the nucleus paraventricularis.

As a quantitative measure of the physiological vacuolization, the total percentage of vacuolized ganglion cells has partly been used, and partly the percentage of large-vacuolized cells (i.e. containing vacuoles broader than the Nissl-zone). The latter quality having the advantage of making the difference between the control group and the group of delirious patients stand out more clearly, as the large vacuoles are mainly found in individuals exposed to protracted severe stress.

Material examined: This consists of a control-group of 14 patients who—in comparison with the delirious group—died suddenly or rapidly without symptoms of preceding long-lasting severe stress (and especially no dehydration or delirious

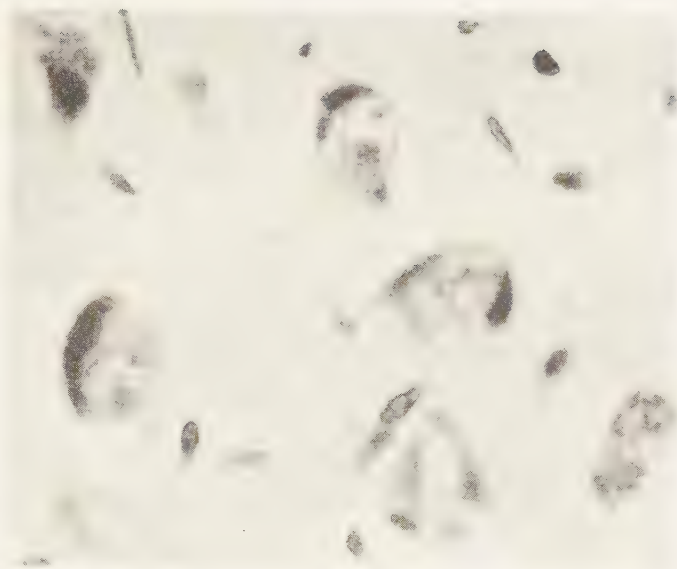


Fig. 2.

Normal supraoptic ganglion cells. Control brain H. 114. Gallocyanine stain, pH 1.64 $\times$ 900.

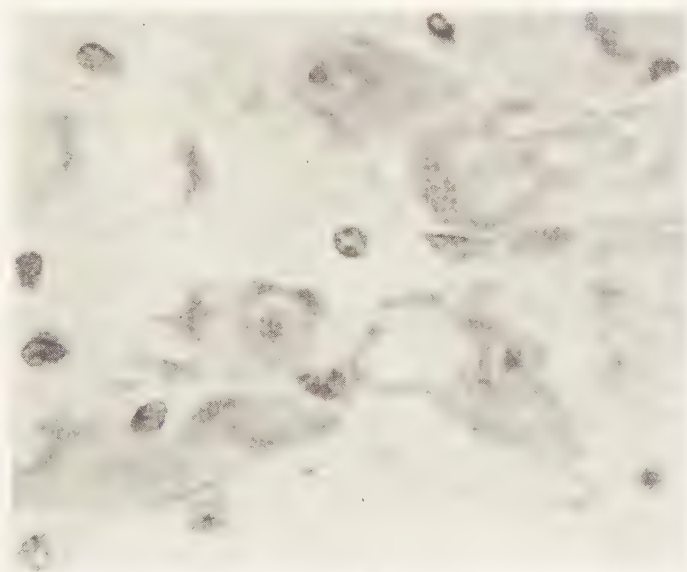


Fig. 3.

Supraoptic ganglion cells from a fatal case of delirium acutum. Pronounced swelling. Intense chromophobia. Notice the large vacuoles in the three most centrally placed ganglion cells. Brain P. 808. Gallocyanine stain, pH 1.64 $\times$ 900.

DIAGRAM OF RESULTS

Control group: 14 cases of rapid death.

Brain no.	Sex and age in years	Cause of death and clinical disease	Terminal somatic stress in minutes (approximately)	Percentage of vacuolized supraoptic ganglion cells	
				Total %	Large-vacuolized cells %
P. 042	♂ 55	Paralysis cordis, resectio ventriculi, ulcus ventr.	60	20	4
P. 0370*	♂ 61	Paralysis cordis, laparotomia explor., angina pect., diabetes mell. ...	120	7	1
P. 805	♂ 22	Vulnus sclopetarium abdominis, laparotomia	180	9	2
P. 828	♂ 30	Vulnus sclopetarium cerebri	20	17	8
H. 114	♀ 57	Embolia a. pulm., depressio ment. endogen. (med. gr.)	30	10	2
H. 143	♀ 36	Embolia a. pulm., mania (l.-med. gr.)	30?	37	5
H. 328	♀ 50	Paralysis cordis, psychosis psychogen.	10	12	6
H. 599	♀ 68	Embolia a. pulm., fract. mall. ext. seq., psychopathia	10	10	1
H. 649	♂ 53	Embolia a. coronar., schizophrenia paranoid.	5-360 ¹	11	4
H. 717*	♀ 75	Paralysis cordis, schizophrenia vet.	3	13	3
H. 728	♂ 72	Paralysis cordis, arterioscl. cordis, schizophrenia vet.	30	14	4
H. 861	♀ 50	Embolia a. pulm., mb. cordis mitral., mania (l. gr.)	270	11	2
H. 953	♂ 68	Paralysis cordis, depressio mentis senilis (l. gr.)	40	13	1
H. 1194	♀ 43	Hæmorrhagia magna cerebri, hypertensio art., schizophrenia vet.	10	8	1
Average	52.9 years	Control brains	83.8 min.	13.7± 2.0%	3.1± 0.6%

¹ i.e. the exact moment of exitus is not known, but death has probably occurred within an interval of 6 hours.

reactions),—and a delirious group comprising 36 patients having died of delirium acutum after protracted severe psychic and somatic stress.

The control-group includes 4 psychically normal patients who died in consequence of an accident or operation, and 10 mainly calm psychiatric patients who died of intercurrent somatic syndromes. This group does not, of course, pretend to be normal material, but just a comparison-group which is characterized by the fact that the intensity, and the duration of the terminal stress (incl. the agony) is reduced to a relative minimum in proportion to the delirious group.

For want of space it has been necessary to omit a report on the histories of the cases (which are to be published elsewhere) and only to state the number, sex, age, clinical disease and cause of death (as regards the acute deliria the last-named is not specified, however, as it is nearly always a question of exitus in consequence of circulatory insufficiency). Furthermore is given a rough estimate of the duration

Delirious patients—36 fatal cases of delirium acutum.

Brain no.	Sex and age	Etiology ¹	Terminal somatic stress in days (approx.)	Vacuolization	
				Total % vacuol. cells	% large vacuol. cells
P. 847	44	E. 1. Scarlatinae seq.	11	21	11
P. 857	38	E. 1. Puerperium	14	13	1
H. 763	41	E. 1. Strumectomiae seq.	6	30	14
H. 1043*	63	E. 1. Commotio cerebri	10	27	18
H. 1137	19	E. 1. Mongolismus, catarrhalia	4	31	20
P. 682	36	E. 2. Puerperium	50 60	26	12
P. 813	50	E. 2. Struma	9	29	14
P. 822	22	E. 2. Puerperium & lactation	10	16	5
P. 837	55	E. 2. Erysipelas seq.	12	56	40
P. 858	31	E. 2. Puerperium febrilis	5	15	4
P. 885	18	E. 2. Malnutritio	4	12	5
H. 408	21	E. 2. Angina tonsillaris	7	46	36
H. 765	26	E. 2. Encephalopathia spastica	4	16	7
H. 936	49	E. 2. Abdominalia ac.	14	17	10
P. 886	74	E. 3.	5	20	9
H. 260	70	E. 3.	6	43	15
H. 977	59	E. 3.	9	23	14
P. 800	39	E. 4.	8	35	20
P. 808	41	E. 4.	13	54	40
P. 821*	55	E. 4.	8	31	19
P. 864	42	E. 4.	12	19	7
P. 875	18	E. 4.	10	15	3
P. 879	52	E. 4.	19	39	20
P. 884	37	E. 4.	12	28	14
P. 921	46	E. 4.	10	29	17
P. 922	40	E. 4.	10	26	17
H. 215	38	E. 4.	6	12	3
H. 1034	40	E. 4.	14	35	24
P. 758	57	E. 5.	14	48	26
P. 799	49	E. 5.	8	26	14
P. 881	58	E. 5.	6-10	48	21
H. 654	56	E. 5.	7	23	5
H. 656	58	E. 5.	8	36	17
H. 684*	57	E. 5.	7	24	9
H. 723	67	E. 5.	8	32	19
H. 1028	54	E. 5.	11	42	24
Average	45.02 years	Delirious brains	10.7 days	29.0 ± 2.0%	15.4 ± 1.6%

¹ E. 1.: Mainly exogenous etiology.—E. 2.: Combined exo-psychogenous etiology (only the endogenous noxa being mentioned).—E. 3.: Endogenous etiology (i.e. acute delirium as a fatal complication of an endogenous psychosis, in all 3 cases mentioned a delirious mania).—E. 4.: Mainly psychogenic etiology.—E. 5.: Cryptogenous (i.e. probably mostly psychogenous) etiology.

² If the somewhat lower average of age in the delirious group might be supposed to influence the vacuolization, this effect should, according to *Scharrer* (1940, 1945) and *Watters* (1935-36), be very insignificant, and rather cause a slight decrease in the vacuolization. Consequently the pronounced preponderance of vacuolization in the delirious group cannot depend on the rather slight difference in age.

of the terminal somatic stress (i.e. the period of clinical signs of stress such as hyperpyrexia and/or dehydration and/or circulatory insufficiency). Usually, however, the delirious patients have been under stress for a considerably longer time, but the exact beginning of the psychic strain is rather difficult to establish, and very likely this is the reason why it has not been possible by means of the named rough estimate to find any certain correlation between the duration of the terminal stress and the degree of vacuolization.

Finally the degree of vacuolization has been stated in the two last columns of the diagram, the former indicating the total percentage of vacuolized ganglion cells in the nucleus supraopticus, and the latter the percentage of large-vacuolized cells.

COMMENT

From the material published it appears that usually considerably more and larger vacuoles are found in the supraoptic (resp. paraventricular) ganglion cells of the delirious brains than in the control group. A statistical valuation of the material correspondingly proves that there exists a distinctly significant difference in the degree of vacuolization between the control-group, which is characterized by a short terminal stress with relatively few preagonal stressors (among which especially no dehydration or fever and, usually, only a moderate psychic strain), and the acute deliria, characterized by numerous severe and long-lasting terminal stressors¹ (among which, especially, severe psychic strain, hyperpyrexia, dehydration, and hypoxia).

This decidedly indicates that the character and intensity of the terminal stress is determinative of the degree of vacuolization in the supraoptic (and paraventricular) ganglion cells so that it has finally been possible to establish a relation between the terminal clinical syndrome (in the present case delirium acutum) and the human neurosecretory activity changes,—and, furthermore, the findings in man under stress appears, as was expected, to be analogous to the investigations on animal-material, carried out especially by *Bargmann*, and collaborators.

According to these authors as well as to *Verney* it seems most reasonable to presume that the two inevitable noxae, the osmotic disturbance (i.e. dehydration), and the emotional strain, are the most prominent neurosecretory stimuli in acute delirium. Finally, there also seems to be a possibility that the terminal hypoxia might be a contributory factor.

¹ For instance possibly preceding infectious, febrile, or endocrine disease, puerperium, lactation, hemorrhage, etc. (i.e. in the exogenous deliria) causing disturbances of the fluid-balance, furthermore severe psychic strain, somatic exhaustion in consequence of the psychosis, hyperpyrexia, dehydration, and terminal shock-condition with hypoxia.

For want of space, no detailed account has been given in the present paper of the other activity-changes of the ganglion cells i.e. especially the conditions of the Nissl bodies, which are to be dealt with in a later publication. It should be emphasized, however, that increase of vacuolization is usually followed by decrease of the Nissl-material, reaching its climax in the intense chromophobia of the acute delirium as an expression of a progressive exhaustion of the ganglion cells.

SUMMARY AND CONCLUSION

A comparison of the neurosecretory activity-states in the ganglion cells of the human supraoptic nucleus (determined by a rough quantitative estimate of the physiological vacuolization of the ganglion cells) in non-delirious patients, having died rapidly without prolonged stress—with the corresponding conditions in patients who died of delirium acutum, after protracted severe psychic and somatic strain, (i.e. especially emotional excitation, dehydration, hyperpyrexia, and hypoxia) indicates that both the character and the intensity of the terminal stress is determinative of the degree of vacuolization, resp. of the neurosecretory activity changes.

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THE ELECTROENCEPHALOGRAPHIC PATTERNS IN YOUNG HEALTHY CHILDREN FROM 0 TO FIVE YEARS OF AGE

*Their Practical Use in Daily Clinical
Electroencephalography*

By

SVEN BRANDT, M.D. and HELGA BRANDT, E.E.G. Technician

At the present time the clinical value of electroencephalography depends entirely upon comparative findings in large groups of patients and in "normal" individuals. The electroencephalographer must learn by experience what is normal and what is abnormal. In normal *adults* the different patterns during the waking stage and at the various depths of sleep are fairly constant and easily identified. Learning to recognize these patterns can be accomplished within a short time by any person working with electroencephalography. In *older children and adolescents* some irregularities in the dominant frequency are normal. This was pointed out in 1944 by *Henry*, who after careful study of 540 records of normal children, between four and 19 years of age, felt he had reason to warn against making too definite conclusions from observations of lower-than-alpha potentials in records of children with various psychological abnormalities (behavior problems, delinquency, etc.).

In *children under five years of age*, standards for normality in the electroencephalographic picture are much less constant. This refers not only to the dominant waking frequency, which is one of the measures ordinarily used in clinical electroencephalography; but also to the presence of paroxysmal high-voltage slow frequencies in the records, which is a frequent normal finding in drowsiness at the ages of one and one-half to six years.

Fig. 1 gives an impression of the gradual change in dominant frequency with age. This model, however, gives no information about the range of variation within each age group or the allowable variation in

Maturation of Occipital Frequency with Age.

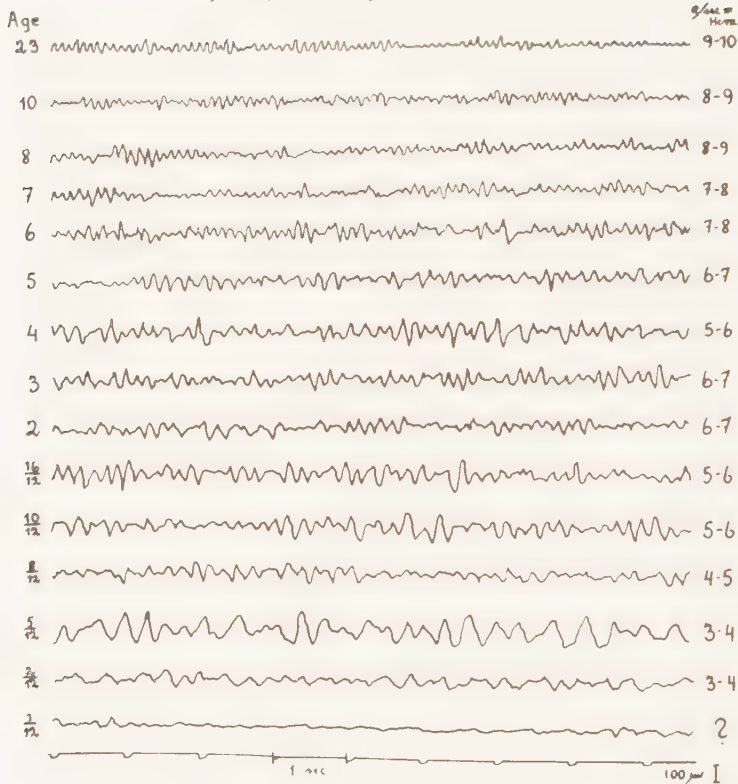


Fig. 1.

Occipital frequency during waking phase at different ages.

each individual at a certain age. Standards of mean dominant frequency, in children at different ages, and its range has been given by *Lindsley* (1939), *Bernhard & Skoglund* (1939), *Henry* (1944) and *Larsson, Melin, Öhrberg & Öhrberg* (1939). Such standards, however, give no information about the amount of interspersed lower frequencies at a given age. This information can be calculated by cumulating along a centimeter scale any potential with a frequency below 7.5 per second found within one meter samples. Standards for such measures—called per cent-time-delta values—are given by *Henry* (1944) for occipital and central regions. The normal range is rather large. Thus, for 15 children, nine years of age, *Henry* found a mean occipital per cent-time-delta value of 12.93 with a range from 1.8 to 39.2. Surprisingly enough *Henry* found the same large variation—0.8–29.8—in a much older age group (18 years).

MATERIAL

Tables showing normal standards like those mentioned above are of some value when properly used in an electroencephalographic laboratory where children are frequently examined. Nevertheless, we felt a growing need, especially in the case of very young children, for a method making it possible to compare *directly*, without too much waste of time, a given dominant frequency with a certain amount of representative normal records. For this purpose, records were collected from 111 children, 0 to five years of age. We soon discovered that the most ideal standards for clinical "normality" had to be abandoned, if we hoped to gain any results based upon a reasonable number of cases during a reasonable period of time. Practically all children have received a bump on the head at some time during their early life and these could not be discarded as "abnormal" for this reason. With few exceptions, patients from the hospital wards were not used. The reason for this was that we wished to avoid any change in the electroencephalogram, which might be caused by generalized acute or sub-acute disorders, even when such were apparently not localized in the nervous system. For similar reasons we did not include children admitted for chronic abnormal conditions or deviations from generally accepted normality (intellectually retarded children, children with behavior problems or with allergic manifestations, etc.). For children outside these categories, we adopted the following condition:

There must have been no convulsive symptoms at any period in the life of the proband, his parents or siblings. (This could not be stated with certainty in regard to the unknown fathers of 29 children from an orphanage).

METHOD

Most children were examined in both the waking and sleeping stages. A six-channel ink-writing Kaiser-electroencephalograph was used. At least ten children were used for each of the following 10 age groups:

0-3, 4-6, 7-12, 13-18 and 19-24 months and
2-2½, 2½-3, 3, 4 and 5 years.

Records of ten children were selected from each group and cut-outs were arranged as follows: two 10-second samples—chosen from parts of the record taken when the child (according to clinical judgment) appeared to be awake—were taken from each record. One sample, referred to as A, was considered representative for the dominant waking frequency in the child. The other sample, referred to as B, represented

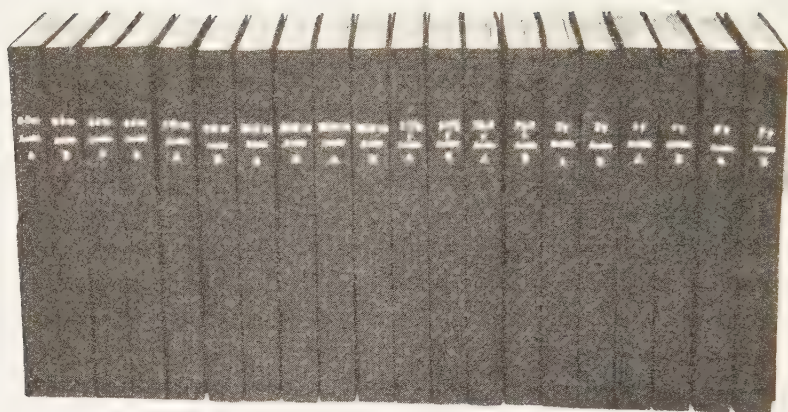


Fig. 2.

For explanation see text.

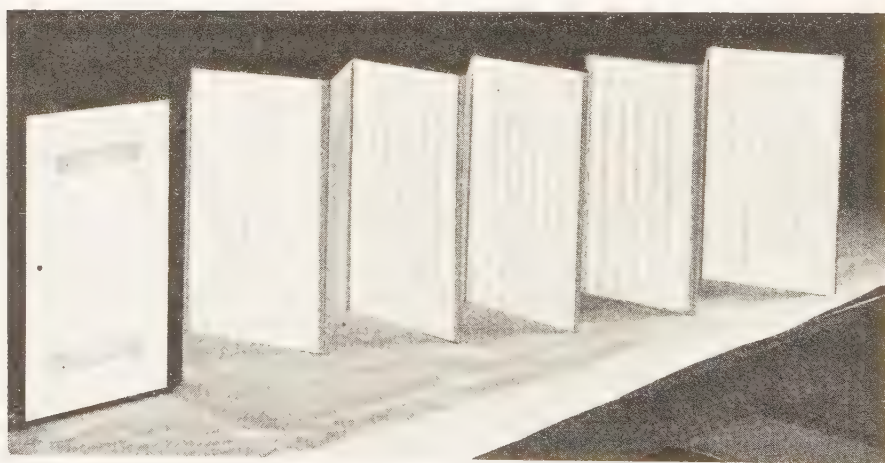


Fig. 3.

For explanation see text.

those parts—where available—which contained the highest amount of potentials of lower frequencies than the dominant rhythm. Samples A and B were then pasted to corresponding pages in two cardboard accordion books each being 10 pages long (Figs. 2 and 3).

Thus, by unfolding these two books, A and B, a snapview impression of normal frequency range can be obtained as well as an impression of the amount of slow frequencies that may be found interrupting the dominant rhythm at a given age (Figs. 4-6).



Fig. 4.

Corresponding pages, showing the average dominant frequency in two children, 3 years of age (left, accordion book A) as well as parts of the record where interspersed slow frequencies were found (right, accordion book B).

Note: In the child—O.S.S.—no such slow frequencies could be found in the record.



Fig. 5.
Variations (upper two records) or lack of variation (lower records) found in waking rhythm in two children—4 years of age.



Fig. 6.
Variations found in waking records of two children—18 months of age (left book A, right book B). The findings in the lower left record may be caused by beginning drowsiness.

HYPNAGOGIC HYPERSYNCHRONY

The electroencephalographic pattern during drowsiness in small children differs remarkably from the waking pattern. This shift may be very gradual and some children may show the slower frequency of the drowsy phase at a time where no clinical sign of drowsiness can be detected. We acknowledge the fact that the slower frequencies demonstrated in accordion book B may have been caused, in some cases, by such an onset of "non-detectable" drowsiness. Therefore, in a given



Fig. 7.

Severe hypnagogic hypersynchrony of continuous type in an 18 month old girl.

child, suspected of abnormal patterns, we always, in order to be quite sure of our facts, follow the gradual shift from the waking phase to sleep so that the typical drowsy pattern can be fully developed and later compared with the waking phase before or after sleep.

The changes occurring in small children during drowsiness have been called "hypnagogic hypersynchrony" by Kellaway & Fox. This finding is in great contrast to the well known reduction in the electrical activity found in adults. The pattern is characterized by slowing of frequency (4 per second or slower) combined with an increase (mild,

moderate or severe) in voltage, which is comparatively larger in the frontal and central-parietal areas than in the occipital regions. The finding is not obligatory. That is to say that an adult pattern may be found in a certain percentage of such children (about 30 %); when present it may be of two types, continuous (46 %) or paroxysmal (24 %), although transitional types are not unusual. Examples are shown in Figs. 7, 8 and 9 B and D. Fig. 10 shows the distribution at

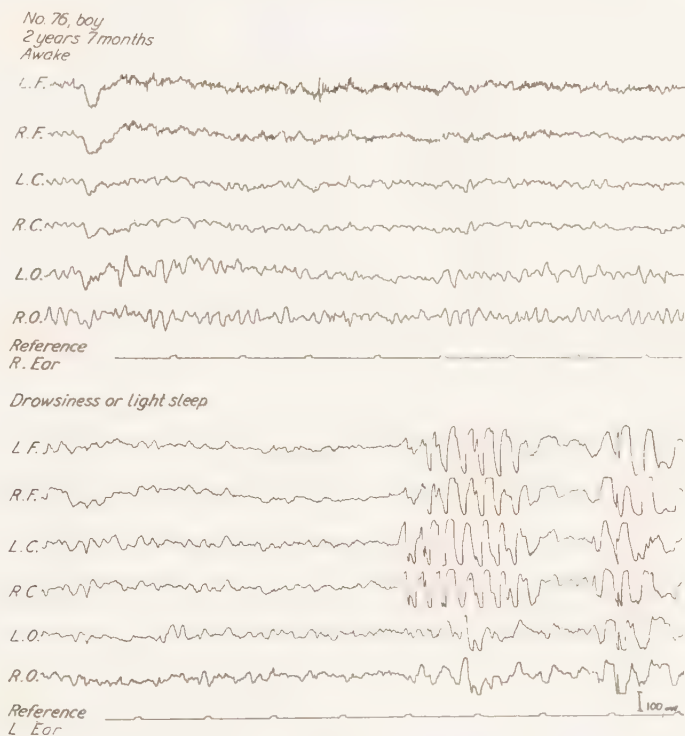


Fig. 8.

Severe paroxysmal hypnagogic hypersynchrony (borderline abnormality?) in a 2 $\frac{1}{2}$ year old boy.

different ages of types and grades of this hypnagogic hypersynchrony as found in our material. The electroencephalographer must be completely familiar with this normal pattern, since when well-developed and paroxysmal, it may be indistinguishable from abnormal paroxysmal discharges, specific for epilepsy. As a matter of fact, there are some instances where no definite decision can be made regarding normality or abnormality in a given case (Fig. 8). Therefore, one must be extremely careful when drawing diagnostic conclusions from paroxysmal

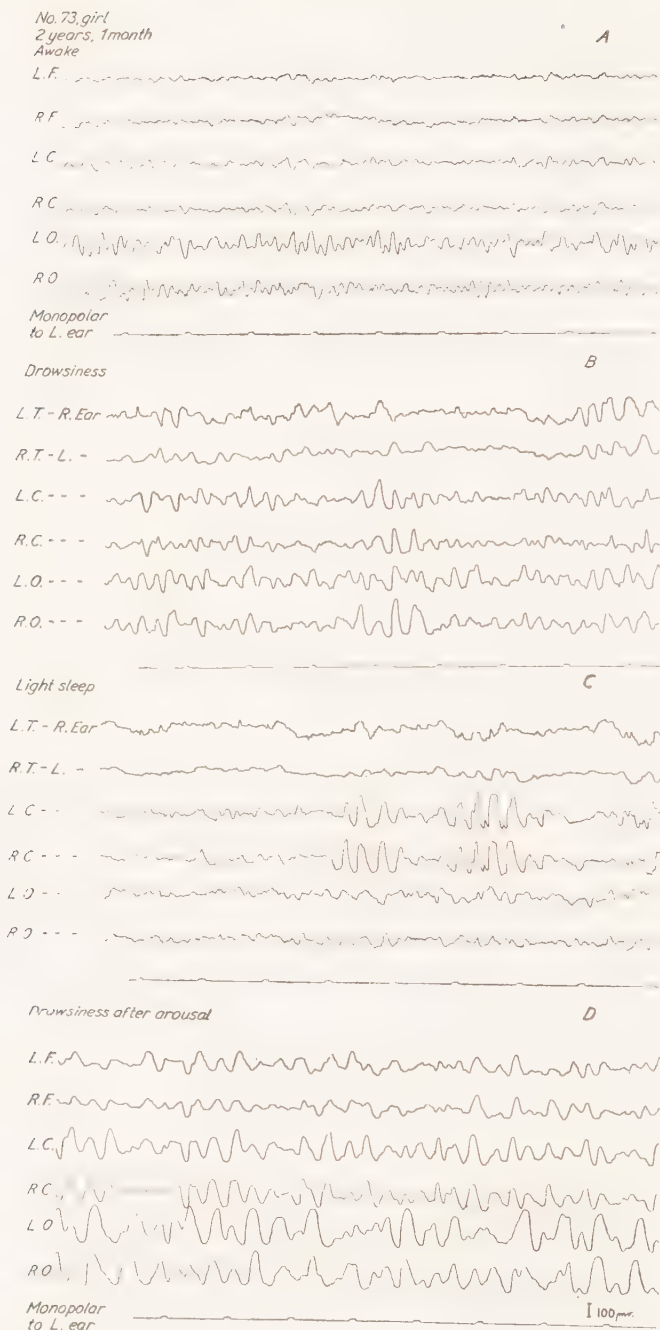


Fig. 9.

Shift of electroencephalographic pattern in a 2 year old girl at various physiological stages.

A: Awake.

C: In light sleep.

B: Drowsy.

D: Drowsy after arousal.

(Note the pronounced slowness in the occipital regions in D)

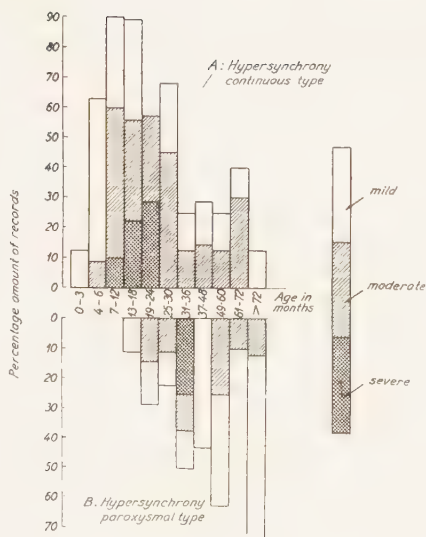


Fig. 10.

Percentage representation of various degrees of hypnagogic hypersynchrony in 71 records from normal children at varying ages. Further 32 records (18 from babies 0-6 months of age) showed no hypersynchrony.

discharges in the records of small children, where such disturbances appear in the drowsy phase *alone*.

OTHER PAROXYSMAL DISCHARGES REPRESENTING NORMAL FINDINGS

The *sleep spindles* during light sleep (Fig. 11), appearing first in the central-parietal, later in the frontal leads, should never cause diagnostic confusion. Their appearance and shape (in small children) does not differ fundamentally from the well known picture in adults.

The paroxysmal hypnagogic hypersynchrony may gradually decrease in amplitude and extension when real sleep begins and may then change into the other well known paroxysmal sleep pattern also seen in older children and adults: *The bi-parietal and bi-central humps* (Fig. 9 C).

In small children the immediate electroencephalographic *response upon awakening* is usually a very pronounced hypersynchrony with slow high-voltage frequencies dominating all parts of the record. It is especially important to know that this hypersynchrony may continue in the occipital leads alone for a longer period before a full waking pattern has returned (Fig. 9 D).

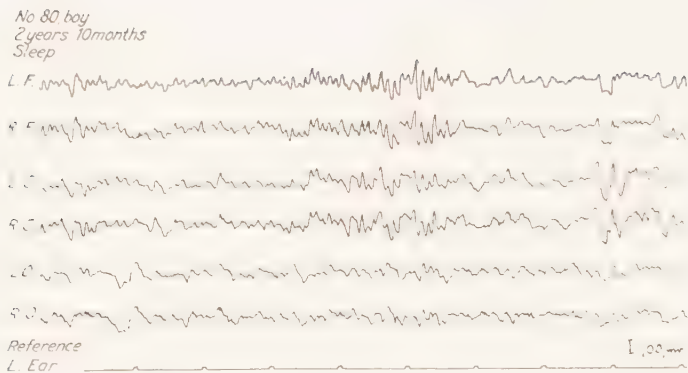


Fig. 11.

Bifrontal and bicentral spindles during light sleep in a boy approximately 3 years old.

ABNORMAL RECORDS IN THE "NORMAL" MATERIAL

A certain number of abnormal records must be anticipated in material from clinically healthy persons. *Gibbs, Gibbs & Lennox* found abnormal records, both mild and severe, in 16 % of those taken from 1000 individuals. *Henry* found abnormal records in 5 % of 583 children and adolescents and 6.9 % "questionably normal".

In our opinion, at least 4, perhaps 5, of our 135 records of normal children (including 24 children over five years of age) should be classified as abnormal. A moderate diffuse dysrhythmia was found in two 5 year old boys. Abnormal paroxysmal activity was found in one or two, the first a 3 year old boy admitted for masturbation. Finally, a well defined spike focus was found in one temporal region in a 4 year old boy who had had a head injury two years earlier. From an electroencephalographic point of view this child must be surmised a potential epileptic.

SUMMARY AND CONCLUSION

Various sources of diagnostic confusion in clinical electroencephalography of young children have been described. A practical method for the rapid employment of normal waking records in daily electroencephalographic work has been elaborated. The relative representation of various types of changes during drowsiness, found in 135 children from 0 to 6 years of age, have been registered (Fig. 10). The authors warn against making diagnostic conclusions (in the records of small children) from paroxysmal activity found during drowsiness alone.

Four or five records from 135 healthy non-epileptic children from 0 to 6 years of age without known epileptic disposition were classified as abnormal.

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We are extremely indebted to our former assistant technician, Mrs. Poula Hansen, for her careful and patient assistance in the recording of the tracings.

VALUE OF BRAIN MICROSCOPY FOR THE CLINIC OF THE VARIOUS FORMS OF MENTAL DEFICIENCY

By

G. V. BREDMOSE and ERNA CHRISTENSEN

In the daily work in an institution for mental defectives the patients are divided into groups according to the degree of their intellectual deficiency.

On the basis of genetic investigations and anamnestic information, familial and non-familial groups may be set up, and according to their clinical features a part of the patients may be referred to the group of congenital cerebral dysplasias, that is, to embryonal arrest of development that need not be hereditary.

In recent years, increasing attention has been paid to the exogenous factors in fetal life (German measles and toxoplasmosis) and, above all, to the paranatal anoxia, as the cause of irreparable changes in the central nervous system. It is not always practicable on the basis of entirely clinical examinations to distinguish these groups of diseases from results of embryonal arrest *sui generis*, whereas the post mortem macroscopic and microscopic examination of the brain in many cases will give the differential diagnosis. An account of the frequency of mental deficiency due to exogenous factors, therefore, is of great preventive significance as here is one of the points where active measures may be taken to reduce the number of mental defectives.

Even though similar works have been published previously here in Denmark (Wildenskov and Christensen & Vestergaard) a continued follow-up investigation will still be justified.

Another reason for this is the fact that Krabbe, who has also been interested in arrested embryonal development and disturbances of growth—as is evident, for instance, from his monograph entitled: “Nervelidelser og Vækstforstyrrelser i Barndommen”. Munksgaard,

Copenhagen, 1947 has advocated the establishment of a research institute for mental defectives.

The present work will serve to point out that cooperative studies are now being carried out between special institutions here in Denmark and that efforts are being made through team-work to solve some of the present problems.

In his monograph "Developmental Disorders of Mentation and Cerebral Palsies", C. E. Benda (1952) has given a thorough survey of the developmental anomalies in the central nervous system as well as the exogenous factors which may cause arrest of development or degeneration in early childhood considered from a clinical and pathologic-anatomical viewpoint. Furthermore, in his monograph "Cerebral Anoxia", C. B. Courville (1953) has presented a minutious investigation on the injuries produced by anoxia in fetal life and during parturition.

The purpose of the present work has not been to give any complete survey of the various forms of mental deficiency but to continue the work previously reported by Christensen & Vestergaard (1949), namely:

- 1) to look into the distribution between endogenous and exogenous forms of mental deficiency in an autopsy material from an institution for mental defectives,
- 2) to correlate the histological findings with the various degrees of mental deficiency,
- 3) to compare the clinical diagnoses with autopsy findings in order to see with what certainty the clinical diagnosis may be made, and
- 4) to see what might be the most frequent cause of acquired or exogenous mental deficiency,
- 5) finally, it will be appropriate to consider possible preventive measures that might be taken in order to reduce the number of mental defectives and to discuss some possible forms of therapy –and, perhaps, find out whether some form of therapy may have been neglected in the present cases¹.

Our material comprises 88 patients who had stayed for a shorter or longer period in the Andersvænge Institution where they had all died.

As is evident from Table 1, the material comprises altogether 9 simple-minded, 25 imbeciles and 54 idiots. On the basis of the histological findings they are divided into two main groups:

¹ All the genetic studies were carried out in the University Institute of Human Genetics, Copenhagen (Chief: Professor T. Kemp, M.D.).

1) congenital mental deficiency: 45 cases, and

2) acquired mental deficiency: 36 cases.

Finally, among the 9 simple-minded there are 7 in whom no histological sign of congenital or early acquired changes in the brain could be demonstrated.

From this tabulation it will be noticed that the number of idiots is greater among the congenital forms than among the acquired forms, namely, 33 out of 45 cases as against 21 and 35 among the acquired forms.

On looking into the genetic aspects and the available information concerning pregnancy and parturition, many interesting things are found.

In *Group 1 a* (congenital cerebral dysplasia), among 23 cases 9 have a family history of disposition to hereditary mental deficiency. Of these 9 patients 6 belong to the group of imbeciles and simple-minded, while only 3 out of 14 idiots have a history of familial mental deficiency or congenital defects. On the other hand, in 7 other cases in this group of idiots there are findings indicating exogenous injuries during pregnancy or parturition. In 3 of these cases labor was protracted and the child was apparently stillborn with asphyxia for up to 45 min. One was delivered through cesarean section 2 months before term because the mother had convulsions the last 10 days of pregnancy, and in 3 cases the microscopy showed ganglion cell dysplasia with varying degrees of immature ganglion cells and lacking stratification, together with degenerative changes in the form of gliosis and ganglion cell atrophy, besides senile changes with depositing of amyloid bodies and accumulation of lipofuscin in the ganglion cells. Two of these cases are particularly interesting: both girls, 18 months old, idiots, thriving poorly, and died from cerebral hyperpyrexia. The mother of one of these girls was poorly and confined to bed throughout pregnancy. In her child the development of the brain appeared to have been arrested in the 5'-6' month of fetal life as here there is merely a suggestion of gyrus formation, complete absence of stratification of the ganglion cells in the cortex and merely a suggestion of myelinization of the white substance (Fig. 1). The mother of the other girl had a serious infection with an unknown virus in the 8' month of pregnancy. In her child the gyrus formation is normal but the stratification in the cortex is lacking and the ganglion cells are immature. In the third case—an idiot, 10 years old, with spastic tetraplegia, torsion spasms and symptoms of slight bulbar palsy—information is obtained about protracted delivery and apparent still-birth, and here the microscopy showed ganglion cell dysplasia in the cortex and also gliosis

TABLE 1

Schematic Survey of the Patient Material.

// signifies complicated birth. () signifies hereditary taint.

Group	Simple-minded	Imbecile	Idiots	Total
Ia Congenital cerebral dysplasia	/0/ 1 (0)	/0/ 8 (6)	/7/ 14 (3)	/7/ 23 (9)
Ib Mongolism		/1/ 3 (1)	/3/ 9 (6)	/4/ 12 (7)
Ic Tumor of brain			/2/ 3 (3)	/2/ 3 (3)
Id Tuberculous sclerosis			/0/ 2 (1)	/0/ 2 (1)
Ie Dandy-Walker's syndrome			/0/ 4 (2)	/0/ 4 (2)
If Leuko-encephalopathy			1 (0)	1 (0)
Total in Group I	/0/ 1 (0)	/1/ 11 (7)	/12/ 33 (15)	/13/ 45 (22)
IIa Porencephalia		/2/ 4 (2)	/4/ 5 (4)	/6/ 9 (6)
IIb Status marmoratus		/2/ 2 (0)	/4/ 5 (0)	/6/ 7 (0)
IIc Pachymeningeosis	1			1
IId Infectious or post-infectious lesions ...		/2/ 3 (1)	/0/ 5 (2)	/2/ 8 (3)
IIe Atrophy of unknown origin	/1/ 1 (1)	/1/ 4 (1)	/2/ 6 (3)	/4/ 11 (5)
Total in Group II	/1/ 2 (1)	/7/ 13 (4)	/10/ 21 (9)	/18/ 36 (14)
III Leukemic and senile changes	/1/ 6 (4)	/0/ 1 (1)		/1/ 7 (6)
Total—Groups I, II and III	/2/ 9 (5)	/8/ 25 (12)	/22/ 54 (24)	/32/ 88 (42)

round the 4th ventricle and the central canal in the spinal cord. Everything considered, it also appears as if her mental deficiency and the neurological symptoms of her cerebral cortex have developed after birth injuries.

An imbecile man, aged 65, who died of bronchopneumonia, had been suffering from chorea and involuntary weeping since childhood.

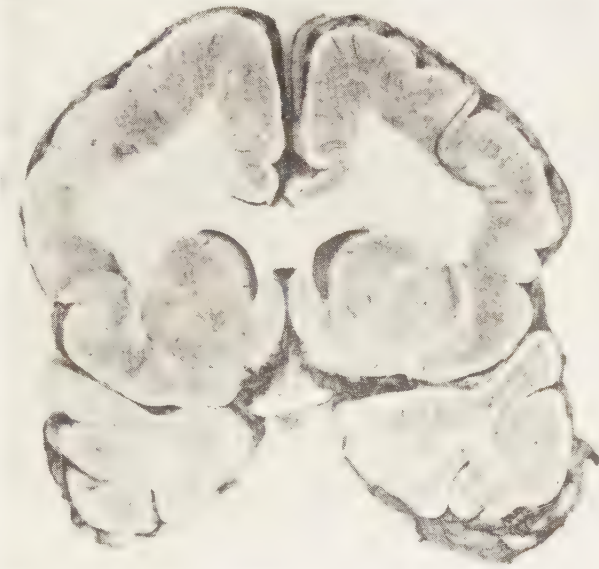


Fig. 1.

Coronal section through the brain from a 18-months old idiot (see text).

The clinical examination moreover revealed the presence of bilateral Babinski reflex. He realized that, besides his congenital oligophrenia, he was also suffering from another organic brain lesion, and autopsy revealed the presence of disseminated sclerosis with old plaques localised to the spinal cord. In addition, there were pronounced senile changes with hyalinization of the arterioles in the brain and subpial gliosis, together with the ganglion cell dysplasia in the cortex. He belongs to the group with a hereditary taint.

Among the patients without hereditary taint we find a woman, aged 28, with imbecility, hydrocephalus, spina bifida and paresis of the lower extremities. She died from an infection of the urinary tract and the autopsy further revealed agenesis of the corpus callosum and septum pellucidum besides ganglion cell dysplasia and secondary ganglion cell atrophy. To this group is also reckoned a clinically verified case of phenylpyruvic oligophrenia in an imbecile man, aged 27, who died

of universal metastases from a carcinoma of the parotid gland. It is to be mentioned in particular that the histological examination of his brain showed surprisingly slight changes in the form of slight ganglion cell degeneration in the cortex and hypothalamus.

It should also be mentioned that on one patient—female, 30 years old—without any hereditary taint, the clinical diagnosis was: idiocy, nanism, gargoylism. She was slightly microcephalic (weight of brain: 900 g.) but the histological examination of paraffin sections from the brain showed merely slight ganglion cell dysplasia. By mistake, no examination was made for lipoids and thus the diagnosis has not been verified histologically.

Finally, the histological examination is defective on account of post-mortal changes in the case of a boy, 4 years old, uncleanly, imbecile, with motor restlessness, mutism, nystagmus and strabismus, who died from intracranial hemorrhage after a fall. Autopsy showed megalocephalia (weight of brain: 1475 g.) while nothing can be said about possible histological changes.

The only simple-minded patient in the group of congenital cerebral dysplasias is a man, aged 63, who died of pneumonia and cancer of the rectum and who gave a family history of disposition to mental deficiency. He was microcephalic (weight of brain: 680 g.). Besides congenital changes with ganglion cell dysplasia, the microscopic examination showed also pronounced senile changes with satellitosis and ganglion cell atrophy.

This group includes 2 cases with corpus callosum agenesis. Previously, this anomaly was considered the cause of mental deficiency but since the introduction of air encephalography in the clinic, this anomaly has been observed in many mentally normal persons, and thus it cannot play any role in the mental state of the patient.

Among the idiots, the weight of the brain varied from 1600 g. in a boy of 5 years who was suffering from hydrocephalus to 750 g. in the girl of 18 months who showed absence of gyrus formation. The average weight of the brains in this material is 1070 g.

The age distribution of the patients varied from 52 to 1.5 years, with an average of 20 years. One feature common to the histological findings is a predominant localization of the anomalies to the cerebral cortex.

Clinically, only 2 patients presented neurological symptoms in the form of spastic tetraplegia—and in one case also torsion spasms—but these are the only patients in the group in whom the histological examination has revealed, besides dysplasia, degenerative changes: in 1 patient in the form of gliosis of the 4th ventricle and the central canal

in the spinal cord, in the other, changes in the substantia nigra, as seen after chronic epidemic encephalitis.

In the simple-minded the average weight of the brain was 1292 g., varying from 1550 g. in a man aged 27 to 700 g. in a man, aged 52. The average age was 29 years, the oldest patient being 65, the youngest 4.

As was to be expected, *Group 1 b*, comprising 12 Mongols, shows a pronounced hereditary taint, as in 6 cases there are other mental defectives in the family, psychosis in 2 cases and congenital defects in 1. Four of these patients were born from 2 months to 3 weeks before term, and only in 1 case is there positive information about difficulty in the parturition on account of uterine fibroma in the mother.

The weight of the brain as well as the lifetime are lower for the Mongols than for group 1 a, both of which features show more uniformity, with an average brain weight of 970 g. (variations from 1150 to 620 g.), and the average lifetime for the Mongols is 10 years, the oldest being 31, the youngest 1 year, at the time of death.

In all 12 brains the dysplastic changes are found chiefly in the cortex, with defective maturity and stratification of the ganglion cells, but most of them give an impression of poor myelinization in the white matter.

Only in 1 of these patients, a boy, 2 years old, the possibility of encephalopathy was ventilated clinically on account of his poor general condition, and in his case the histological examination showed also subpial gliosis, that is, degenerative changes in the cortex besides the dysplasia, but no sign of degeneration in the white matter. Also in the case of a girl, 2½ years old, who was born two months before term, subpial proliferation of the glia was ascertained. Whether this might have been due to birth injury or some other exogenous factors could not be decided. Of these 12 patients, 7 died of pneumonia, 1 of pulmonary tuberculosis, 1 with hyperpyrexia of unknown origin, 1 from the sequels of frontal lobotomy, and 1 in an accident. From this it is evident that in the mongoloid patients the resistance to infections is lowered considerably.

Group 1 c comprises 3 patients with tumors of the brain, and all 3 have a family history of hereditary taint. One of these patients was a girl, 2 years old, markedly mentally defective and suffering from epilepsy. In her case the possibility of leukodystrophy was ventilated clinically on account of her progressive illness. Autopsy revealed the presence of an ependymoma filling entirely the right lateral ventricle. Another patient was a boy, 2 years old, also markedly mental defective, with a history of convulsive seizures since he was 1 week old. He was

constantly lying in a posture of opisthotonos. He also had nystagmus and hydrocephalus. In his case too, the possibility of leukodystrophy was ventilated clinically on account of the progressive course of his lesion, but autopsy revealed an enormous astrocytoma involving the entire left hemisphere, infiltrating both the cortex, the white matter, the left anterior horn and the basal ganglia. This patient had been delivered by forceps, and his birth weight was 4750 g. The third patient was a dyscrinic man, 23 years old, with idiocy and hare-lip, and with a history of convulsive seizures from the age of 3 months and, later, violent fits of rage. He was partially cleanly and responded when spoken to. In his case, too, the autopsy revealed a large astrocytoma, located in the septum pellucidum and infiltrating the periventricular tissue round the lateral ventricles, third ventricle, and invading the basal ganglia. In addition, there was a small infratentorial medulloblastoma. All these three patients had a family history of hereditary taint, with mental deficiency in the first two cases and convulsions in the third. As all three patients had had symptoms ever since early infancy, the tumors may be assumed to have been congenital. Still, in No. 3, who died at the age of 23, however, it is more likely that only the astrocytoma has persisted and grown through the many years, while the medulloblastoma presumably has developed later, as a tumor of this kind grows very rapidly.

The 2 patients in *Group 1 d* with tuberous sclerosis were both idiots who died of bronchopneumonia at the age of 15 and 21 years, respectively. Only in 1 of these cases the diagnosis of tuberous sclerosis was made clinically, while in the other merely idiocy and epilepsy were ascertained, together with bilateral optic atrophy. The first patient had a family history with several cases of congenital defects and mental deficiency, while no family history could be obtained in the second case.

Group 1 e comprises 4 patients with Dandy-Walker's syndrome. One of them was also suffering from meningomyelocele which was ascertained immediately after birth, together with persistent pareses of the lower extremities. Particular attention should be paid to the latter condition as in such patients with a special form of congenital hydrocephalus there is a possibility of recovery or, at any rate, improvement of their condition if the diagnosis is made early.

The term of Dandy-Walker's syndrome implies malformation or, rather, absence of Magendie's and Luschkae's foramina with the resulting internal hydrocephalus (Dandy, 1922; Taggart & Walker, 1942; Benda, 1952 and 1954). In some cases the diagnosis can be made already on the peculiar shape of the head of the patient, as the hydrocephalus is localized especially to the posterior horn and the 4th ventricle

(Fig. 2). Provided this lesion is not combined with other congenital defects, the hydrocephalus can be diminished by operation with removal of the fibrous membranes covering the two aforementioned foramina, and if this is done before too extensive irreparable degenerative processes have taken place in the brain, the prognosis is good. Of the 4 patients in our material, 1, who also had meningomyelocele, died at

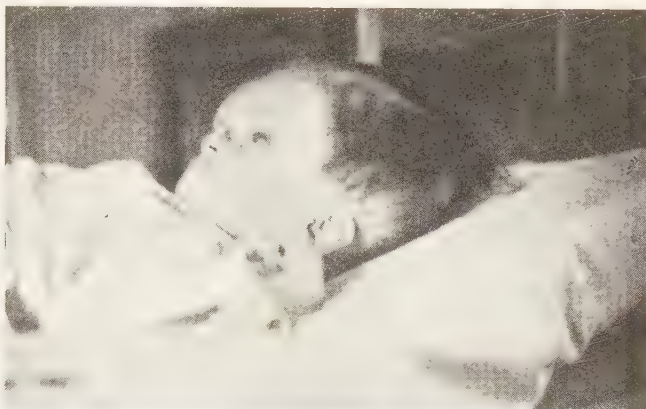


Fig. 2.

5 years old idiot with Dandy-Walker's syndrome dead at the age of 13.

the age of 6 months, while the remaining three lived to be 13-19 years old, and one of them had also a cyst in the septum pellucidum. All four patients were idiots with convulsive seizures and nystagmus, optic atrophy or pareses.

Group 1 f comprises only 1 patient with diffuse sclerosis or leukoencephalopathy. As this case is entered in Einarson & Neel's material, it will not be mentioned further here.

As will be noticed from Table 1, *Group II* consists of patients in whom histologically verified, paranatal, atrophic processes have been the most conspicuous features, and also that here an attempt has been made at a histological classification of the material into subgroups.

Group II a comprises 9 patients, including a single large cyst or cavity as well as polyporencephalic processes, sometimes cortical processes differing in size and accompanied by microgyria, tendency to microcephalia and varying degrees of hydrocephalus. In all these cases the microscopic examination shows arrest of development with lacking maturity of the ganglion cells, especially in the cortex. But the most conspicuous features are the degenerative changes in the form of acute ganglion cell atrophy, proliferation of the glia and decaying processes with depositing of macrophages round the porencephalic processes. In

1 case this affection was combined with stenosis of the Sylvian aqueduct due to ependymitis granularis arising after hemorrhage from birth injuries. This was the case of a boy, 4 years old, with idiocy, epilepsy, spastic tetraplegia and megacolon, who died of volvulus. At the age of one month he went through a serious disease that was diagnosed as serous meningitis. He had been born one month before term. He also had a family history with pronounced disposition to mental deficiency. Also 4 other patients in this group had a family history with occurrence of mental deficiency; and in another case the family history showed a tendency to other congenital defects. In 4 cases, the birth of the patient had been irregular. In one the birth weight was 1500 g. In another, the patient was a twin, and the placenta contained a dead fetus measuring 15 cm. in length. A third patient was delivered through cesarean section. All these patients had convulsive seizures since the first days of life, and they were markedly imbecile or idiots. But, at the same time, they presented evidence of extensive injuries to large parts of the brain beyond the cortex, as here diagnosis were made of Little's disease, spastic hemiplegia, inferior paraparesis, optic atrophy, and deafness. In 3 cases where no information could be obtained about the family history, nothing is known about the course of delivery in 2, while it was very protracted in the third, and the clinical features as well as the autopsy findings were identical with those observed in patients with a hereditary disposition. They all died of febrile diseases, most often pneumonia and bronchitis, and their average lifetime was only 20 years. The oldest of these patients died at the age of 53.

The porencephalic processes are taken to have been of anoxic origin. No matter whether the anoxia appeared in fetal life or at the time of birth, the central nervous system—which is not completely formed in this period of existence—shows a tendency to cystic decay with reactive secondary gliosis, which explains the tendency of the symptoms to progression.

The fact that at the same time there is a lacking maturity of the ganglion cells in some of these patients may also be explained as attributable to exogenous injury. It is rather unlikely, however, that there is also a dysgenetic factor of significance, for, as mentioned, 6 of these patients had a family history of pronounced hereditary taint suggesting that children with hereditary congenital cerebral dysplasia are particularly susceptible to anoxic damage in the form of porencephalia.

Group II b, comprising 7 patients with status marmoratus, differs in various ways from Group II a, as here there was no hereditary dis-

position in any of the patients. Four of them had a history of troublesome delivery with following asphyxia, 2 were born six weeks before term, and in the last case no information could be obtained about the course of delivery. All the patients had convulsive seizures since the first days of life. They were all markedly imbecile or idiots, and 6 of them had also tetraplegia, paraplegia, hemiplegia or double athetosis.

Examination of the brains showed microcephalia in 4 cases, varying degrees of microgyria with more or less pronounced ganglion cell dysplasia in the cortex, fibrosis of the leptomeninges and, as a common feature, poor myelinization with status marmoratus or status dysmyelinatus in the white substance, which explains the neurological symptoms. Finally, it is to be mentioned that in one of them—male, aged 22, who died with cerebral hyperpyrexia—there was also kernicterus (extracellular and intracellular depositing of yellowish pigment in the basal ganglia). Unfortunately, nothing is known about the Rhesus type in him and his mother. Also these patients died at an early age of cerebral hyperpyrexia or infection of the air passages. In all these cases the exogenous factor—difficult delivery resulting in anoxia—appears to have been the cause of the mental deficiency and the neurological symptoms.

Group II c comprises only 1 patient, a simple-minded male, who died suddenly at the age of 52. Since early childhood he had had epilepsy and hydrocephalus with craniostasis and flattening of the sella turcia. Brain autopsy revealed pronounced thickening of the dura with a layer of new-formed, vascular, connective tissue on the interior surface, so-called pachymeningeosis vasculosa, thickening of the leptomeninges and ganglion cell atrophy and gliosis in the cortex. It seems most likely that the original lesion here has been a bilateral subdural hematoma arising from a traumatic birth injury and since absorbed. But no definite proof of this can be given.

Group II d is polymorphous. A feature common to all the cases here is some form or other of infection. One man who died of croupous pneumonia at the age of 17 was suffering from congenital syphilis with paralytic dementia. He had had convulsive seizures since early infancy, spastic paralysis, and he was stuporous. Brain autopsy showed meningitis with plasma cell infiltration, degeneration and inflammation of the cortex, especially in the third layer of ganglion cells and encephalomalacic processes in the putamen.

No. 2 was a girl who died at the age of 3 years. Both the mother and the patient gave a strong positive reaction for toxoplasmosis. The patient had had convulsive seizures, increasing in frequency, and she was an idiot, microcephalic, with right anophthalmus. Examination of

the brain showed fibrosis of the leptomeninges, frontal microgyria, internal hydrocephalus, calcifications in the cortex, numerous cortical cysts with surrounding gliosis and ganglion cell degeneration, besides formation taken to be pseudocysts with toxoplasmas—though this cannot be stated with certainty. In all probability, this was a case of toxoplasmosis. Among the remaining 6 cases, 2—a woman of 23 and a man of 62—presented both histological and clinical evidence of chronic epidemic encephalitis with progressive neurologic and psychiatric symptoms, and it seems reasonable to assume that the mental deficiency here was acquired, arising as a result of chronic encephalitis.

In a male, aged 65, with a low degree of idiocy and convulsive seizures, who died of purulent bronchitis, the brain autopsy showed microcephalia (weight of brain 690 g.), internal hydrocephalus, microgyria, pronounced ganglion cell atrophy with gliosis and sclerotic white substance, besides pronounced chronic cystic leptomeningitis. Presumably he had meningo-encephalitis in infancy.

Similar features were found in an idiot, aged 2 years, but here microscopy showed more active inflammatory processes in the leptomeninges. Another idiot, aged 18, who died of ileus, and who also had megacolon, showed similar changes in the brain with degeneration of the ganglion cells in the substantia nigra, on which account we also arrived at the conclusion that the original affection had been meningo-encephalitis. This assumption finds support in the circumstance that the patient had been normal at birth and that further development ceased in the first month of life while, at the same time, he commenced to have convulsive seizures.

Whether the last case in this group involves an infection alone or, besides, some birth injury, is a question that cannot be settled with certainty. He was an idiot with amaurosis and spastic tetraplegia, and he died at the age of 20 with hyperpyrexia of unknown origin.

Autopsy showed microcephalia, microgyria, ganglion cell atrophy and gliosis together with rather pronounced hydrocephalus and fibrosis of the leptomeninges and, at the same time, moderate ganglion cell dysplasia in the cortex.

Only in 2 of these cases did the family history include a single instance of mental deficiency, and in none of the cases was there any positive information obtained about difficulties at the parturition.

Group II c comprises 11 patients in whom the common feature at the examination of the brains was found to be atrophy of some sort or other, while only 3 showed slight dysplasia, and 2 imbecile men, aged 60 and 68 respectively, presented depositing of lipofuscin in the ganglion cells, atheromatous and arteriosclerotic changes in the vessels. It

may be that in most of these cases the changes resulted from a previous attack of meningo-encephalitis, as now there was fibrosis of the leptomeninges, subpial gliosis and ganglion cell atrophy, besides in some cases also ependymitis granularis on the walls of the ventricles, but none of them showed any active inflammatory process. In 7 of them the autopsy showed moderate microcephalia with a brain weight of 750-960 g., and all of them were adult imbecile or idiots with symptoms persisting from early childhood, while they all had a history of normal spontaneous delivery, though 4 were born 4-6 weeks before term. Three patients had a family history with a single instance of mental deficiency.

Group III, as mentioned before, is made up of 7 patients, 6 of whom were simple-minded and one imbecile, and all died at the age of 54-80 with exception of one simple-minded with myelogenous leukemia who died at the age of 25. No congenital abnormalities were found in these patients, merely senile changes in the form of senile atrophy, encephalomalacic processes, depositing of lipofuscin in the ganglion cells and arteriosclerosis besides—in the 25-year-old patient—leukemic infiltrations in and round the vessels. Only the last-mentioned patient had been delivered by means of forceps. In the remaining 6 cases, as far as is known, the delivery had been normal. On the other hand, 5 of the patients in this group have a family history of disposition to mental deficiency.

Sex distribution. Of the patients in the present material, 49 were males, 39 females, with preponderance of males in all the groups except in that of congenital dysplasia where the proportions is 11 males/12 females, and among the Mongols with 5 males 7 females. But the individual groups are all too small to allow of any particular significance, being attached to the sex distribution.

The *average age* at exitus was 60 years for the simple-minded, 32 for the imbecile, and 16 years for the idiots.

DISCUSSION AND CONCLUSION

Even though the accuracy of placing our individual patients in the different groups may be discussed, the above analysis illustrates the significance of correlating the clinical features, the genetic data and the microscopic findings in the brain of mental defectives, as such considerations will lead us beyond the attitude that the institutions for mental defectives are merely asylums for intellectual defectives.

As was to be expected, the hereditary factor is seen to play a role

especially in the congenital cerebral dysplasia and mongolism. But it is surprising to see that there is also a pronounced hereditary taint in the group of porencephalics, where the lesion in itself is exogenous, namely: of anoxic origin. As previously pointed out, this indicates that children with congenital cerebral dysplasia are markedly susceptible to damage from birth injury in the form of porencephalia.

The account of the present material does not allow of any definite stand being taken with regard to possibly extended indications for provocation of abortion on an eugenic basis, but it speaks in favor of this question being taken up for renewed consideration through further investigations.

Like previous investigations of the same kind, our material shows that, above all, it is in the field of obstetrics that particular effort should be made to reduce the frequency of mental deficiency. Birth injuries—especially in the form of anoxia—play a decisive role in the development of the severe forms of mental deficiency, and it is characteristic that this type of patients also presents many neurological symptoms indicative of damage to the basal parts of the brain, which is confirmed by histological examination.

There can hardly be any doubt that a more extensive prophylaxis with regard to hypoxia during the parturition and active intervention of the obstetrician in the presence of already manifest anoxia will reduce the number of these sad cases of mental deficiency in which no effective therapy is practicable once the damage to the brain has developed.

In cases of some serious infection in the mother during pregnancy—especially virus infections—the advisability of provoked abortion should also be considered seriously. Our material includes two children in whom time of the congenital arrest of development could be ascertained, and correspondingly their mothers had acquired serious infection at the very time concerned.

That also infection in the central nervous system in infancy is of significance to the development of mental deficiency is evident from the fact that the present material includes 8 patients reckoned as belonging to this category.

Effective therapeutic intervention may be made only in a relatively few cases—above all, in patients with Dandy-Walker's hydrocephalus, which is due to lacking formation of Magendie's and Luschka's foramina and the resulting progressive internal hydrocephalus. The pre-supposition for recovery of such patients through operative opening of these foramina, however, is the absence of other malformation of the central nervous system and at the hydrocephalus at the time of birth

is not so large that irreparable damage has been done to the brain. Among our 4 patients with this anomaly one was submitted to operative treatment but could not be cured as he also had a lumbar myelomeningocele.

In the 3 patients with tumors of the brain, no operative treatment would have led to recovery, as the tumors infiltrated such large parts of the brain that total extirpation was out of the question; and from the case histories it is evident that the tumors must have been inoperable already at the time of birth.

Thus, as is evident from our material, systematic neuropathological studies in connection with genetic investigation concerning mental defectives can actually give valuable information about, and principles for, prophylactic measures and, although in a lesser degree, for therapeutic measures in such cases.

SUMMARY

On the basis of neuropathological studies covering 88 mental defectives who died in the Andersvænge Institution (9 simple-minded, 25 imbecile and 54 idiots), these cases are classified into pathologico-anatomical groups.

There are 45 cases of congenital mental deficiency, to which are reckoned 23 cases of congenital cerebral dysplasia, 12 patients with mongolism, 2 with tuberous sclerosis, 3 with tumor of the brain, 4 with Dandy-Walker's syndrome and 1 case of leukoencephalopathy.

The group of acquired mental deficiency comprises 36 patients, including 9 with porencephalia, 7 with status marmoratus, 1 with pachymeningeosis, 8 with postinfectious lesions, and 11 with atrophy of unknown origin.

Finally, there are 7 mental-defectives without histologically demonstrable evidence of congenital or early acquired changes in the brain.

Particular stress is laid upon the significance of birth injuries, especially anoxia, to the severe degrees of mental deficiency combined with neurological symptoms.

Mention is further made of increased obstetrical prophylaxis, the danger of virus infections in the mother during pregnancy, and operative therapy in cases of Dandy-Walker's syndrome.

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CEREBRAL PEDUNCULOTOMY IN FOUR CASES OF HYPERKINESIA

*(Three cases of choreoathetosis and one of
rhythmic tremor)*

By

BENDT BROAGER

In 1949 A. Earl Walker introduced a new operative procedure, cerebral pedunculotomy, in the treatment of hyperkinesia.

In a case of hemiballismus an excellent effect was seen of this operation, which was performed as a partial transection of the pyramidal tract at the cerebral peduncle contralateral to the involuntary movements. At the price of a very slight loss of power of the affected side a satisfying result was gained as only small occasional twitchings were left of this violent hyperkinesia when the patient was seen again one year after the operation.

It seems from the literature on the treatment of hyperkinesia that pedunculotomy has been tried in rather few cases at all, especially in cases of choreoathetosis.

In a survey of the surgical treatment of involuntary movements, in 1952, Walker mentions that pedunculotomy has been tried in two cases of choreoathetosis without satisfactory results. Better results were seen in seven cases of the Parkinsonian syndrome, as the rhythmic tremor was much alleviated in several patients; in two of these tremor was abolished for more than two years, but at the price of a marked hemiparesis.

In 1953 Hamby reported on three cases of dystonia musculorum deformans treated by surgical interruption of pathways at several levels in the central nervous system. One child was treated by bilateral serial cerebral pedunculotomy with resulting abolishment of dystonia and athetoid movements. Although quadriplegia followed the operation, the state of the child was very much ameliorated. Cortical

ablations and cauterization of the ventral column of the cervical spinal cord were used in the two other patients.

Estimating the results, Hamby concludes that cerebral pedunculotomy, in his opinion, is the method of choice as the results are more favourable and the side-effects less disabling than after the cortical excisions. In an addendum after the submission of his manuscript Hamby mentions the treatment by bilateral pedunculotomy of two additional children with dystonia, with similar results to that in the case reported on in his paper.

In 1953 Boixados published a case of choreoathetosis treated (by Obrador Alcaldes and Gonzales Mariscal) with a good result with cerebral pedunculotomy. Five months after the operation a very slight hemiplegia was present with complete abolishment of the involuntary movements.

Cerebral pedunculotomy has been performed by the author in the treatment of four patients, three of them suffering from choreoathetosis, with results which seem to encourage the use of this surgical procedure in cases of athetoid involuntary movements.

CASE REPORTS

Case 1 (Univ. Hosp. Nkir, 17126) was a 36-year old man who for four years had been suffering from a progressing disseminated sclerosis. On account of pronounced ataxia of the lower limbs he was unable to stand or walk without help from several persons. During two years a rythmical and coarse tremor had developed in the right arm. The tremor was present at rest but it was extremely intensified at even slight movements and then including, too, the whole of the right side of the body; the tremor was now completely dominating and making his state more and more unbearable.

He was slightly demented, slightly euphoric and in a bad state of nourishment. Ocular movements were nystagmoid and optic papillæ pale. Reflexes were atypical as abolished abdominal reflexes and positive Babinski signs were seen with abolished deep reflexes of the lower limbs. He was completely bedridden.

A left-sided pedunculotomy was made in April 1951 (Broager). The operation caused no paresis although the tremor disappeared completely for 2-3 months. Then tremor gradually recurred but never to a degree as before operation. Post-operatively tremor has never been a dominating part of his syndrome, of which, however, the other symptoms have been steadily increasing during the following three years, paresis of the lower extremities gradually spreading to the upper ones so that he is now partly paretic in both arms, too.—The patient is at home, his wife taking care of him. It is evident to the family that the operation has greatly alleviated the state of the patient, even if the tremor did recur to a certain degree.

Case 2 (Univ. Hosp. Nkir, 18568) was a 20-year old man with a grave double athetosis of dubious etiology.

His birth was prolonged as the unmarried mother, being alone at the delivery,

in despair and confusion for one whole night with both her hands tried to keep back in her womb the head of the child as it was being born.

During his first year of life it was observed that the limbs were flaccid and moving very little spontaneously.

At the age of one year he fell from a table on to the floor and was unconscious for an hour and a half.

Two years old he was treated in a hospital for a "brain fever" with prolonged drowsiness and high fever.

Since that time athetoid movements started in his whole right side, beginning in the arm. When he was admitted the hyperkinesia had been severe for at least ten years.

During the last six months movements had started also in his left side, of the same type but less than in the right side.

He was completely unable to take up a normal position. All muscles of the right side of his body took part in the slow and extreme movements of the fingers, arm and leg which were almost constantly altering his position. Constant contraction of antagonistic muscles were present. The facial muscles took part in the movements. Slow spasms of the spinal erector muscles often would force him into opisthotonic postures. Less intense spasms of a like type were present in his left side. All involuntary movements stopped during sleep. All muscular spasms were less intense under the influence of alcohol.

The spasms very much resembled dystonic torsional spasms. However, the articulations showed no capsular contractions, and muscular atrophy was present in the legs to some degree only.

He lived in his home. During the day both right extremities, at least, were fixed with broad bands to his bed, or, if he was trying a sitting position, to his chair so that the involuntary movements would not land him upon the floor. Mentally he was slightly retarded as he had not been able to attend school in a normal way, but his intelligence was not poor. In spite of complete sphincteric control motions of the bowels were a daily problem as he was not able to stay on a bed-pan or a water closet for even a short time.

A left-sided pedunculotomy was done in January 1952 (Broager). At the operation a small arterial branch must have been cut at the deepest part of the incision, as bleeding of an arterial colour occurred for a short time when this was performed.

The involuntary movements disappeared completely for two years but during the last six months before the control in October 1954 very slight movements have recurred in the right upper extremity.

Postoperatively he had a complete right hemiparalysis of several weeks standing. Slowly and gradually it has subsided somewhat, but two years and eight months after the operation he still presents a very pronounced right hemiplegia.

Irrespective of the operation the involuntary movements of the *left* side have gradually continued to increase, and are now almost as severe as those of the right side before pedunculotomy was done. The left-sided movements are more dystonic than was seen in the right side, as the same positions may be kept on for longer periods.

Cerebral pedunculotomy on the right side will now be performed.

Case 3 (Univ. Hosp. Nkir, 18770) was a 30-year old woman who at the age of thirteen had been taken ill by *encephalitis* with bilateral papilloedema of 3 4

diopeters, with a crossed hemiplegia including a right facial palsy of peripheral type and a left spastic hemiparesis, and with a left-sided hemi-hypæsthesia.

A decompressive craniotomy was made in the right temporal region, and for some time the decompression was bulging considerably. During this period X-ray treatment was given, and gradually the papilloedema subsided as did the prominence of the decompressive region.—Since then she presented a left homonymous hemianopia, a left-sided hemiplegia and a tendency to Jacksonian motor epileptic fits in the left side, starting in the upper limb. Four years later she began having athetoid involuntary movements of the left upper extremity.

When she was admitted to the neurological department her life had for 13 years been dominated by the involuntary movements which, together with the hemiplegia of the affected side, made her a complete invalid.

Her left arm, hand and fingers were constantly moving, slowly and painfully, from one extreme to another, but she was able to arrest the movement of the arm with the other hand. If she tried to use the right hand in eating, drinking, writing etc. it was constantly disturbed by the movements of the left one. Besides, she presented neurological findings corresponding to her story: Pale optic papillæ, left homonymous hemianopia sparing central vision, oculogyral instability, slight left facial palsy as part of a left spastic hemiplegia, with rigidity, which made walking impossible. The rigidity of the left arm was of the cog-wheel type. There was, further, a left total hemi-hypæsthesia, left astereognosis and abolished sense of position peripherally in the left extremities. Psychically she seemed normal.

Lumbar pneumoencephalography showed dilatation especially of the right lateral ventricle, the whole system being drawn somewhat to the right.

Her symptoms were assumed to be the result of encephalitis with papilloedema and brainstem-symptoms, combined with atrophic lesion of the right hemisphere which had been pressed severely outwards through the decompressive craniotomy at the time of increased intracranial pressure.

Pedunculotomy was performed on the right side in March 1952 (Broager).

A left hemiparalysis was present postoperatively for one week, after which it gradually subsided to end in the same degree of hemiplegia as before operation.

The involuntary movements have permanently disappeared, as well as the rigidity. She is now, 2½ years after the operation, living in an asylum, very happy about the result of the operation. She is able to use her right hand freely at meals, and also for writing, plaiting, weaving and the like. She is, however, still unable to walk on account of the old left-sided hemiplegia.

Case 4 (Bispebjerg Hosp. Nkir. 514) was a 11-year old boy who from the age of four to eighteen months had been admitted to a pediatric hospital for congenital heart disease with paroxysmal tachycardia, the heart action rising to 300 a minute. The attacks was treated with strophantine and gradually subsided upon continuous treatment with digitalis.

At the age of 3½ years he was found one morning with a right hemiplegia and blood in the cerebrospinal fluid on puncture. He was observed for a couple of months, part of the time in a neuromedical department, on a diagnosis of emboliæ hemispherii sin. sequ.

Five years old he was treated for almost one year in an orthopedical hospital with different operations on the right lower extremity, after which walking was quite good.

At this time choreoathetoid movements started in his right arm. For the last year before admission to the neurosurgical department his sound left hand had

been almost constantly occupied in arresting the involuntary movements of the right arm and hand. Only for very short periods he was able to use his left hand in a normal way.

His appearance was dominated by the slow, athetoid movements of the right upper limb, alternating between maximum flexion and extension in the elbow and fingers. The wrist was constantly fixed in maximum volar flexion. One extreme position might be held for 30-60 minutes before constant movements carried on



Case 4.

One week after cerebral pedunculotomy. No involuntary movement

again. If he did not use his sound left hand in arresting the hyperkinesia of the right one, it might present small soft movements, somewhat parallel to the athetoid ones of the other hand. Rigidity of the cog-wheel type was present in the right arm. The right leg was slightly paretic and spastic, slightly shorter than the left one, with a positive Babinski sign. Mentally he was somewhat retarded.

Pneumoencephalography showed a slight dilatation of the left lateral ventricle. Plain X-ray pictures of the skull, carotid and vertebral angiograms were normal.

His symptoms were assumed to be the result of an embolus in the left cerebral hemisphere in connection with his congenital heart disease.

Cerebral pedunculotomy was made on the left side in September 1953 (Broag). On awakening after the operation he had a right hemiparalysis. The next morn-

ing he was moving his leg and in the afternoon the arm, too. One week post-operatively he was up and walking and was sent home.

Nine months after the operation involuntary movements were still absent; but in the last two-three months before control in October 1954 very slight movements have recurred in the right hand and fingers.

They do not dominate as before operation and he can freely use his left hand. He can open and close his right hand, but slowly on account of some contraction of the antagonists. He can move his right hand as far as to the posterior part of his neck.

He is happy about the result of the operation.

TECHNIQUE

Cerebral pedunculotomy was performed with the technique of *Walker*: The temporal lobe is cautiously elevated. The lateral surface of the cerebral peduncle is then visualized just above the medial edge of the tentorium. The incision is made from the sulcus lateralis mesencephali and forwards for 1-2 centimeters and with a depth of 6-7 millimetres.

At the first of these four operations the incision was made to a depth of 5-6 millimetres only; abolishment of the tremors was only transitory. In the second case the incision was 7-8 millimetres deep and bleeding occurred from the deepest part of the incision; a grave hemiparesis followed, perhaps on account of the vascular lesion in this region.

In the two last cases incision was performed at a length of 12-14 millimetres and a depth of 7 millimetres, with satisfying results also after an observation time of two years and one year, respectively.

The incision should be compared with that of *Hamby* in the case cited above. Hamby incised the anterior one-third of the cerebral peduncle to a depth of 5 millimetres, in a 12-year-old child. The dystonia was abolished and spasticity somewhat relieved.

In the case of *Boixados* incision in the peduncle was made as in the first case of *Walker*, length twenty and depth six millimetres, and beginning just anterior to the lateral sulcus.

Walker has tried slightly different incisions in cases of rythmical tremor.

The optimum length and depth of the incision in cerebral pedunculotomy has not yet been determined, and will of course be different in children and grown-up persons.

Furthermore it is not quite clear if the incision is best made from the lateral sulcus and forward, or if it should be placed more anteriorly in the basis pedunculi.

COMMENT

In each of the four patients involuntary movements were a dominating part of the syndrome presented; furthermore the hyperkinesia was completely dominating their daily life. In such cases operative treatment may be indicated even at the price of some loss of power in the affected side.

As to other operative procedures in cases of choreoathetoid movements great experience has been had by *Pulnam* with high cervical chordotomies, sectioning or cauterizing the ventral columns in more than 30 cases reported on. Results were fair as the movements were much alleviated in more than half of the cases. In no case, however, the involuntary movements were completely abolished.

Ablations of parts of the motor cortex have been used by many surgeons since *Horsley* introduced this method for choreoathetosis in 1909. Results have varied much, a good deal of them being less satisfactory or only transitory. The same may be said of the ablations of premotor cortex with or without neighbouring parts of the precentral gyrus.

Best relief of the involuntary athetoid movements have mostly been seen with marked hemiplegia. This holds good, too, of the technique of *Schürmann*, who has introduced an almost complete hemisection of the cervical spinal cord for invalidating hemi-athetosis.

In the light of the results with these different methods it seems of interest that one of the three patients mentioned here having choreoathetoid movements as the dominating part of the syndrome presented was completely relieved of the hyperkinesia with an observation time of $2\frac{1}{2}$ years. In the two other cases movements were completely relieved for two years and for nine months, respectively, but after these periods very slight movements recurred.

The treatment with cerebral pedunculotomy was considered definitely worth while in these four cases of hyperkinesia.

It is important that recurrence of involuntary movements may be observed, although very slight, even after a period of complete abolishment of two years after operative treatment.

As stressed by several authors, the periods of observation in patients treated surgically for involuntary movements, must be at least two years before one can rely upon the ultimate results of the treatment.

Surgery of the different forms of involuntary movements is still in a rather experimental phase. Even a small series of patients treated

with fair results may be of some value when trying to understand the syndromes elicited by striatal dysfunction, and when planning a suitable treatment in such cases.

SUMMARY

Cerebral pedunculotomy has been performed in four cases of hyperkinesia.

In one patient unilateral rythmical tremor was a dominating symptom in disseminated sclerosis. Postoperatively tremor disappeared for some months, and then recurring, but never to a degree as before operation.

Of three patients with choreoathetosis one was completely relieved of this symptom, which was the dominating one of the syndrome presented, with an observation time of 2½ years. One patient having double athetosis was treated by unilateral pedunculotomy with resulting abolishment of involuntary movements in the corresponding side for two years, after which a very slight recurrence of movements was observed. In the third case choreoathetoid movements of one upper limb disappeared for nine months postoperatively, after which time a very slight recurrence was seen.

In the case of double athetosis the result in the side treated was gained at the price of grave hemiplegia. In the other cases only very slight loss of power was seen.

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ON BASIC ASPECTS OF THE BLOOD-BRAIN BARRIER

By

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The existence of a blood-brain barrier (BBB) has been discussed for more than 40 years; it has been criticized or even rejected by some investigators, though most have preferred not to adopt a definitive attitude. Increased visible evidence produced by the dye-test technique in animal experiments with artificial cerebral lesions together with demonstrable differences between the central nervous system (CNS) and other organs regarding the rate of penetration of various substances (e.g. ions of various kinds) from the blood stream, have been accepted by an increasing number of investigators as convincing evidence of a barrier, normally restricting the passage of certain substances from the blood to the CNS.

The literature bearing on BBB-problems is rapidly increasing. Broadly speaking, the different papers may be grouped into the following three categories:

1. Investigations of certain details, concerning disturbances of the BBB demonstrated in certain lesions and diseases of the CNS by the use of special test substances.

2. Methodological problems studied by means of different substances, normally showing a restricted passage from the blood to the CNS. At the same time an increasing number of observations have been made which contribute to a clearer conception of the term "BBB".

3. Analytic investigations of the fundamental question whether the theory of a BBB will stand criticism and, if so, how the BBB-effect can be explained. Extensive speculations are often based on few experimental data.

As to investigations of the third category no unanimity has been attained. Does a BBB exist? If so, what is the relation between the BBB and the blood-cerebrospinal fluid-barrier (B-CSF-B)? What is the underlying mechanism of the BBB-effect and to what morphological structure should this mechanism be attributed?

The theory of a BBB is based on the following observations:

1. Certain dyes (e.g. trypan blue, fluorescein)—apparently possessing an electronegative charge in water solution at blood pH (“acid dyes”) (21)—will on intravenous, subcutaneous, or intraperitoneal injection readily permeate into all organs of the body with the exception of the CNS (1, 8, 11–20, 22, 23, 29–31, 33, 34, 36, 38–39). The penetration of the dye into the CNS may be either poor, as in experiments using finely dispersed dyes (e.g. fluorescein), or absent, as in experiments with coarsely dispersed dyes (e.g. trypan blue) (36). If, however, the dye is injected into the subarachnoid space and thus allowed to reach the surface of the CNS, it diffuses over a broad front into the tissue (22, 36).

As exceptions to this rule the dye may pass from the blood into certain small regions of the intact CNS, e.g. in the neurohypophysis and tuber cinereum, in the choroid plexuses (36), and through the main branches of the large basal arteries (17). In most unhealed lesions of the CNS-parenchyma the dye will, moreover, pass freely into any region with damaged tissue (17).

2. The distribution of certain salt ions (e.g. Br , J , PO_4) in the body shows differences in the concentration ratios between the CNS on one hand, the blood and other organs on the other, with a slower penetration rate into the CNS and a lower concentration in the CNS, when a steady state has been reached (26, 32, 40–41). With labelled ions (radioactive isotopes) these investigations have won recognition during the last few years, and have also given rise to new suggestions on the formation of the cerebrospinal fluid (essentially tissue fluid from the CNS?) (5–6, 40–41). Essentially similar results have been obtained in experiments with certain other crystalloids (e.g. glucose (32), sulphonamides, antibiotics). In experiments with artificial lesions of the CNS, it has been shown that these salt ions as well as acid dyes penetrate more readily into the region of such lesions.

Some substances with a specific effect on synapses seem to belong to the same category of substances with a restricted passage into the CNS, possibly indicating a biologically important role in the mechanism of the BBB. In an analogous way the CNS seems to be protected from the influence of certain toxins and from the invasion of certain viruses (21).

All these arguments may seem conclusive as evidence of a BBB, but *certain objections* may nevertheless be put forward. The most important critical comments will now be discussed:

A. Theoretically, a restricted passage of certain substances from the blood to the CNS can be caused by various factors, possibly in combination:

(a) The permeability of the vascular intima-membrane (11-20, 21, 23, 36).

(b) The permeability of the pia-glial membrane (possibly in combination with an active transport mechanism) (24, 38-39).

(c) The absorption capacity of the blood constituents (above all the proteins) as compared with that of the tissue elements (12, 29-31).

(d) The effect of the metabolism in the CNS tissue on the substances studied (6).

If the problem is extended to include the passage of substances into the nerve cells, there is, of course, an additional factor:

(e) The permeability of the nerve cell membranes (1).

If the absorption factor (c) were of great importance, it would be inadequate to use the term "barrier". If more than one factor is of importance, it would be more appropriate to speak of a *BBB-system* than of a BBB.

B. Even if the existence of a barrier for the passage of certain substances is accepted, there still remains the fact that some other substances are able to pass very quickly to the CNS (e.g. water, several narcotics and anaesthetics) (21, 32, 36), and it is still unknown whether some of them might be able to pass into the CNS more readily than into other organs. If this be the case, it would mean a mechanism facilitating rather than hindering the passage of these substances.

Neither is it known whether a restriction of the passage in one direction may denote a similar restriction in the opposite direction or if it may be the effect of an active transport mechanism, facilitating the passage in this opposite direction.

If these theoretical possibilities are to be taken into account, the use of the word "barrier" must be restricted to a certain substance in a defined direction in every case.

It is apparent that a discussion of the BBB-problem should preferably begin with the statement that it is a complicated equation in great need of reduction. *It would perhaps be wise to prefer the term "BBB-system" instead of the common word "BBB"* (11).

Bearing in mind the above-mentioned objections to the current idea of a BBB, *some experimental data and their significance for the BBB-problem will now be discussed.*

I. *Experiments with dyes have the advantage of yielding information not only about the possible existence of a barrier but also of its site.* As some dyes (e.g. trypan blue) do not pass into the CNS even if injected i.v. in considerable amounts, they are very suitable for such experiments. In the experimental animal the relation of the dye to the

vascular wall and the brain tissue can be closely studied in different ways—with and without rinsing the blood vessels (from their coloured contents) during life (observation of the pial vessels) or post mortem (in slices of the brain).

The fact that no dye passes into the normal brain, even if the amounts injected into the blood are large enough to guarantee a considerable amount of free diffusible (not protein-bound) dye substance, or if the brain vessels are perfused with a protein-free dye solution, strongly suggests the existence of a true barrier (12, 17). In any case, as far as this dye is concerned, it can be stated that the protein-bound, non-diffusible portion cannot be responsible for the barrier-effect (17). It should furthermore be specially stressed that in experiments with inspection of the intravitaly exposed brain surface a leakage of stained blood from a damaged vessel will invariably stain the brain surface, although the dye has the same concentration and must be protein-bound to the same degree as in the circulating blood (17).

The fact that the dye does not penetrate from the blood through the pial vascular wall (outside the brain) but readily passes into the CNS-substance when injected into the subarachnoid space or applied direct to the exposed brain surface, likewise proves that the pia-glial membrane cannot be of any significance as a barrier in experiments with such dyes, but strongly suggests the vascular wall as the barrier (12, 17).

The fact that no dye remains in the vascular wall after rinsing the vessel argues strongly for the intima of the vessel being the barrier (17). The objection to this assumption that the rinsing fluid (saline or Tyrode) may wash out the dye from the wall is contradicted by the following two observations. In studies of the pial vessels *in vivo* or shortly post mortem (*in situ*) it has been shown that the wall of the vessel is unstained immediately by rinsing (17). If, however, a pial or brain vessel is slightly damaged, for instance by air emboli (14), the vessel wall will remain stained after the rinsing procedure. Objections can therefore rather be raised to all experiments in which the vessels are not rinsed, because the dye is then allowed to penetrate into the vascular wall post mortem (when, owing to anoxia or the fixing agent, e.g. formalin, the barrier has ceased to function).

Further observations pointing to the vascular endothelium as the site of the barrier in the dye experiments are also on record. Thus, histopathological studies have shown that the abnormal passage of the dye into the vascular wall in the presence of asphyxial lesions in the new-born is correlated to pathological changes of the vascular endothelium (23). Furthermore, it has been demonstrated that a toxic

lesion resulting in passage of the dye substance through the pial vessels can be caused by lower concentrations of the toxic agent if it is applied to the intima-side of the vessel instead of the adventitial side (18).

Finally there is the theoretical point of view that if it can be regarded as established that the barrier-effect is linked to the vascular wall and not to the pia-glial membrane, it is reasonable to assume it to be the result of the permeability-determining membrane of the vessel, i.e. the intima.

As a conclusion of these different facts and observations it appears that, as far as dyes are concerned, there is a true BBB and that this barrier is ascribable to specific permeability properties of the cerebrospinal vessels. I have, therefore, proposed to speak of the vascular permeability in the CNS and of tests for studying disturbances of this permeability rather than of a BBB, as this term often seems to be confusing (17). This way of looking at the matter does not exclude the possibility of physiological variations or even slight pathological disturbances of the vascular permeability, not demonstrable with a special dye-test (e.g. trypan blue) (8). If, however, the disturbance of the cerebro-vascular permeability is of such a degree that plasma proteins are able to pass, the dye substance will certainly pass as well. Certain observations seem to indicate that a marked passage of dye may occur also in slight lesions without noticeable passage of the plasma proteins (14, 17). Wide experience with the dye-test technique has strongly supported the validity of the statement that pathologically important disturbances of the cerebrovascular permeability can always be demonstrated with a correct technique, in vivo or post mortem in the experimental animal, and post mortem with the supravital modification of the technique in the human brain (17).

II. *Experiments using ions and other crystalloids showing a retarded and restricted passage from the blood to the CNS* have -after introduction of the isotope technique- yielded important results. It now seems to be generally accepted that the considerable delay in the appearance in the CNS of these substances and then in only strikingly low concentration must be attributed to a barrier-effect, the BBB-system (32, 40-41). Most authors seem to have taken it for granted that the cause of this barrier-effect is the same as in the dye experiments. This conception is, of course, rather natural, but difficult to prove. As the category of substances discussed here is very heterogeneous, there is good theoretical reason for the assumption that various factors are of importance in cooperation with the cerebrovascular permeability (1, 5-6). Some substances may be specially adsorbed to certain tissue ele-

ments or involved in the metabolism of the CNS, and it sounds quite possible that the pia-glial membrane plays some role in their restricted passage. *For the present it may, therefore, be recommendable to use the term "BBB-system" and to analyze every single substance of importance according to the different factors in this system.*

It should be stressed that in experiments with the PO_4 ion the distribution in the brain corresponds fairly well with the results in the dye experiments (no barrier-effect in the choroid plexuses or in the neurohypophysis and the epiphysis) (3, 9). This finding speaks in favour of the identity of the determining barrier-factor in these experiments. On the other hand the microscopical distribution of the PO_4 as well as the Br ions (10, 35) within the brain is not uniform and a certain concentration was observed in special cell layers, indicating that adsorption to certain tissue elements is of importance. The decisive factor may nevertheless be the restrictive cerebrovascular permeability.

As the passage into the CNS is often increased in lesions of the CNS, the substances may also be used as test-substances for demonstrating disturbances in the BBB-system.

III. *In clinical investigations* more interest has naturally been focused on the cerebrospinal fluid (CSF) than on the CNS-tissue. Some investigations have, nevertheless, been made on the CNS-tissue such as in the localization of brain tumours with the isotope technique (34).

The composition of the CSF with special regard to the penetration of certain substances from the blood into the CSF has been the subject of extensive studies and used by most investigators interpreted as a test for demonstrating the presence or absence of a disturbance of the BBB. On the basis of the general conception of the choroid plexuses as the main source of the CSF, together with the fact that the plexuses are strongly stained in dye experiments, I have, however, postulated that the mechanism of the BBB and of the B-CSF-B should be considered as different, although their effect is fairly similar (13). From a theoretical point of view an abnormal passage from the blood to the CSF cannot be considered as always and entirely dependent on disturbances of the BBB. In practice, however, most instances of a pathologically changed composition of the CSF seem to depend on lesions of the vessels in the subarachnoid space and in the surface layer of the CNS and may accordingly, nevertheless, be attributed to disturbances in the BBB-system.

IV. *Investigations of the CSF production* have gained new interest in connection with experiments with the isotope technique (5-6, 40-41). The results indicate that the extracellular fluid of the CNS and

the CSF are of essentially the same composition and much speaks in favour of the CSF originating as tissue fluid from the CNS. The choroid plexuses would then be of minor importance as the source of the CSF. This would imply the elimination of my above-mentioned theoretical objection to CSF-analyses in the evaluation of disturbances summarily in the BBB-system.

V. *Investigations of disturbances of the BBB-system with the use of test-substances* have been discussed above, but the repeated reports in the literature of investigations made without considering the source or errors in consequence of an imperfect technique warrant some critical remarks.

A suitable test-substance should be easily demonstrable and relatively non-injurious (at least to the BBB-system) and a condition necessary for its use as a test substance for the BBB-effect is, of course, that the passage should normally be restricted by the BBB-system. It happens occasionally that investigations are made with substances which are normally able to penetrate readily to the CNS. Such experiments can hardly have any bearing on the BBB-problem, but may, of course, be of interest in other connections. The higher concentration of these substances in the CNS in comparison with the CSF presumably depends on absorption and metabolic processes in the CNS tissue.

As mentioned above, the dye-test technique must be complemented with a rinsing of the vessels and, as a rule, the results should be controlled by histological studies. Otherwise the blood may stain the vascular wall and neighbouring tissue post mortem and thereby provide a serious source of error.

There are many other sources of errors in the dye-test technique that must be controlled. If the injected dye solution is concentrated and prepared with distilled water, a precipitation occurs in the blood, causing microembolism with solid particles. Properly prepared dye solutions in saline may after filtration also show precipitation if they are allowed to stand some time before use. In artificial respiration (sometimes used in the experimental animal) air embolism may occur if the insufflation pressure is too high for the lungs. In all perfusion experiments the risk of air embolism from insufficiently filled tubes may cause false results. A massive staining of the whole brain in experiments with lesions of a reversible nature (e.g. in experiments with carbon monoxide intoxication or with cardiazol convulsions) should always indicate a search for a source of error because lesions of such severity are always fatal.

SUMMARY

The BBB-effect as demonstrated by a restricted passage of certain substances from the blood to the CNS seems to be ascribable to different factors. A closer study of this complex mechanism may lead to the conclusion that the importance of the different factors varies with the substance used. Therefore it is more appropriate to speak of a BBB-system.

With the dye-test technique one important factor in the BBB-system can be studied, the permeability of the cerebrospinal vessels. The endothelium of these vessels seems to possess specific permeability properties. Lesions causing disturbances of the cerebrovascular permeability may be demonstrated in vivo or supravivally by the dye-test technique. Different sources of error must be controlled, otherwise the results will not be reliable.

Investigations by various authors using radioactive isotopes as test-substances suggest that the cerebrospinal fluid is derived mainly from tissue fluid from the CNS. Analyses of the cerebrospinal fluid may, therefore, yield results of importance for demonstrating disturbances in the BBB-system.

The nature of the main factor in the BBB-system, the specific permeability property of the cerebrospinal vessels, is still unknown.

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ACTION POTENTIAL PARAMETERS IN DIFFERENT HUMAN MUSCLES

By

FRETZ BUCHTHAL and POUL ROSENFALCK

Changes in duration, amplitude, and shape of muscle action potentials are used as signs of the degree and the localisation of involvement in neuromuscular diseases. Normative values of these parameters are necessary. Previous papers dealing with the influence of some physical and physiological factors on the action potential parameters concerned the brachial biceps only (*Buchthal et al.* 1954, b and c). There are, however, differences in different muscles (*Petersén and Kugelberg* 1949; *Jasper and Ballem* 1949; *Buchthal and Pinelli* 1951; *Feinstein et al.* 1954, a and b), and it is the aim of the present study to provide data on different muscles for comparison with findings in clinical electromyography.

METHOD

The examinations were performed on 25 normal subjects, ages 20 to 25. A three-channel DISA electromyograph was used for recording of the action potentials at weak effort. Concentric and bipolar electrodes with a core diameter of 0.1 mm. were used for leading off. The electrode tip had an angle of 20° . The electrode impedance amounted to $50-150 \times 10^3 \angle -45^\circ \Omega$ measured at 150 cps. with a voltage of less than 10 mV. Intramuscular temperature was measured thermoelectrically. For obtaining mean values of action potential duration and amplitude the electrodes were inserted at random into the muscle, and 20 to 40 different points were investigated at each examination. For this purpose the electrodes were displaced in steps of at least 3 mm. in order to ensure that the potentials picked up by the electrode originated from different fibres.

The amplifiers had a lower limiting frequency of 2 cps., defined by

3 db. discrimination. The input impedance was 100 M Ω in parallel with 100 $\mu\mu\text{F}$. The differential amplification of amplifier plus electrode was more than a hundred over the entire frequency range of the amplifiers. The noise level of the amplifiers was less than 2 μV r.m.s.

The action potentials were recorded photographically from three 1.5" cathode ray oscilloscopes. A sweep velocity of 100 cm. per sec. and a sweep frequency of 5 cps. were used. The paper speed was 5 cm. per sec.

Total duration and peak-to-peak amplitude of the action potentials were measured. The shape was characterized by the number of phases of the potential.

RESULTS

TABLE 1

Mean duration and amplitude of action potentials from different muscles of normal subjects.

Muscle	Number of action po- tentials	Mean duration ¹	Mean amplitude ²
<i>Concentric electrodes:</i>			
Biceps brachii	185	100 ± 2	100 ± 8
Biceps femoris	417	111 ± 2	126 ± 5
Gastrocnemius	194	94 ± 2	142 ± 8
Tibialis anterior	166	123 ± 3	147 ± 8
Extensor digitorum brevis	210	99 ± 2	262 ± 6
Orbicularis oris sup.	289	56 ± 1.5	67 ± 3
Triangularis			
Frontalis			
<i>Bipolar electrodes³:</i>			
Biceps brachii	488	100 ± 2	100
Triceps brachii	500	113 ± 2	144
Deltoideus	115	123 ± 6	178
Quadriceps femoris	344	112 ± 2	228
Gastrocnemius	351	106 ± 2	122
Tibialis anterior	502	126 ± 2	133
Peroneus longus	336	90 ± 2	178
Opponens pollicis	92	109 ± 4	211
Interosseus quartus	349	129 ± 2	106
Abductor digiti quinti			
Orbicularis oris sup.			
Triangularis			
Frontalis	289	60 ± 1.5	111

¹ Mean duration of m. biceps brachii = 100.

² Mean amplitude of m. biceps brachii = 100.

³ Data collected by Dr. P. Pinelli.

Duration and amplitude: The mean action potential duration and amplitude found in different muscles are given in Table 1, expressed in per cent of those obtained in the brachial biceps.

It is seen that the facial muscles gave a mean duration which was 40–45 per cent lower than that of the brachial biceps (Fig. 1). The mean duration of all other muscles investigated lay between 90 and

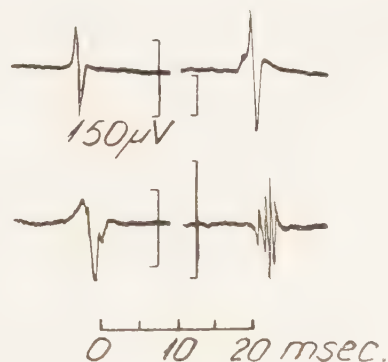


Fig. 1.

Samples of action potentials from facial muscles.

130 per cent of the biceps value. Thus, *m. tibialis anterior* and *m. abductor digiti quinti* showed durations 25–30 per cent above that of the brachial biceps, whereas *m. peroneus longus* gave a mean duration 10 per cent below this value.

The mean amplitudes obtained from different muscles were up to 130–160 per cent higher than that of the brachial biceps, the highest values being found in *m. quadriceps femoris* and *m. extensor digitorum brevis*. Low amplitudes were found in the facial muscles which gave a mean value 33 per cent below that of the brachial biceps (concentric electrodes). Table 1 shows, furthermore, that there is no simple correlation between the mean duration and mean amplitude of action potentials in the different muscles.

Shape: The distribution of the action potentials according to their shape is given for different muscles in Table 2. It is seen from this table that di- and triphasic potentials comprise by far the majority of all potentials recorded (80–90 per cent). Diphasic potentials had their lowest incidence in *m. tibialis anterior*, where on the other hand triphasic potentials showed their highest incidence. The small muscles of the hand and the facial muscles gave the highest percentage of diphasic potentials. In most muscles, polyphasic potentials (≥ 5 phases) comprised only 1–4 per cent of all potentials.

About half of all potentials were smooth and about half irregular, with "knots" and other irregularities.

TABLE 2
Distribution of shape of action potentials.

Muscle	Total number of potentials	Number of potentials (in per cent)				
		Mono-phasic	Di-phasic	Tri-phasic	Tetra-phasic	Poly-phasic
<i>Concentric electrodes:</i>						
Biceps brachii	692	3.0	43.5	41.5	6.5	3.5
Biceps femoris	416	2.0	36.5	47.5	9.5	4.5
Gastrocnemius	194	5.0	43.5	46.5	4.5	0.5
Tibialis anterior	166	2.5	27.0	54.5	7.5	8.5
Extensor digitorum brevis .	213	1.0	34.0	38.5	14.5	12.0
Orbicularis oris sup.	289	2.5	46.5	41.0	4.5	5.5
Triangularis						
Frontalis						
<i>Bipolar electrodes:</i>						
Biceps brachii	488	3.0	47.5	35.5	11.0	3.0
Triceps brachii	500	2.0	41.5	40.5	7.0	9.0
Quadriceps femoris	344	5.0	38.0	44.0	10.0	3.0
Gastrocnemius	351	1.0	41.5	46.5	10.0	1.0
Tibialis anterior	502	4.0	39.0	47.0	7.0	3.0
Peroneus longus	336	2.0	45.0	41.0	11.0	1.0
Interosseus quartus	197	1.0	56.0	36.0	6.0	1.0
Abductor digiti quinti	349	2.0	52.0	38.0	6.0	2.0
Orbicularis oris superior ...	289	4.0	52.0	34.0	9.0	1.0
Triangularis						
Frontalis						

DISCUSSION

The present finding that the mean action potential duration of facial muscles is markedly shorter than that of the extremity muscles is in agreement with previous observations (*Petersén and Kugelberg* 1949; *Jasper and Ballem* 1949). Recently *Björk and Kugelberg* (1953) obtained a mean duration in the extraocular muscles which was only one fourth of that of the first dorsal interosseus muscle.

The longer duration of the motor unit potential compared with the potential of the individual muscle fibre is due to temporal dispersion in the summation of the action potentials from the fibres of the motor unit (*Buchthal, Guld and Rosenfalck* 1954 a). The following factors might contribute to this temporal dispersion:

- 1) the differences in the time of arrival of the nerve impulse to the end-plates;
- 2) the length (Δ) of the region within which the end-plates of the unit are situated;
- 3) the propagation velocities of the different fibres; and
- 4) the length (L) over which the potential is propagated.

Disregarding (1) which owing to the high propagation velocities of motor nerve fibres would be expected to give only a minor contribution, we obtain the following expression for duration:

$$t(L) = \frac{L + \Delta}{V_1} - \frac{L}{V_u} + t_o, \quad (1)$$

where V_u and V_1 denote the upper and lower value of the propagation velocity of the fibres of the motor unit, while t_o is the duration of the action potential of a single muscle fibre. The large motor units must be assumed to have a larger end-plate region and a wider range of propagation velocities than the small motor units. Both of these factors will, as seen from (1), give an increase in duration with increasing number of fibres per motor unit. A correlation of this type has been found by *Feinstein et al.* (1954 a and b). The low mean duration of the extraocular muscles (*Björk and Kugelberg* 1953) is, therefore, attributable to the small size of the motor unit of these muscles (*Torre* 1953). For the facial muscles the same must be assumed to be the case. It was near at hand to assume that it was the length of the muscle which mainly determined the degree of temporal dispersion in the motor unit potential. This is not the case as evident from the high values of duration in the short muscles of the hand and foot as compared with the longer limb muscles. The explanation for the long mean duration in the short muscles must be sought for in a larger spread of the end plates in the direction of the fibres.

While mean duration in the different muscles is correlated to the mean size of the motor unit, the differences in mean amplitude did not depend on the size of the motor units.

As regards the shape of the action potentials it should be noted that m. tibialis anterior which had the highest mean duration also had the highest percentage of triphasic potentials, whereas the facial muscles with their low mean duration had the smallest percentage of these potentials. This correlation between shape and duration has been observed previously (*Feinstein et al.* 1954 b; *Buchthal et al.* 1954 b).

In order to facilitate the comparison of findings in various pathological muscles with those of normal muscle, Table 3 contains the range of normal mean duration, i.e. the intervals of duration within

TABLE 3
Intervals of mean durations in various muscles for the different age groups.
 (Concentric electrodes)

Age of sub- jects (years)	Arm muscles						Leg muscles				Facial muscles
	Deltoidaeus	Biceps brachii	Triceps brachii	Opponens pollicis; interossei quartus	Abductor digi- tini	Biceps femoris; quadriceps	Gastro- cnemius	Tibialis anterior	Pertoneus longus	Extensor dig- itorum	Orbitari- us; supe- rior; trian- gularis and frontalis
0-4	7.9-10.1	6.4-8.2	7.2-9.3	7.1-9.1	8.3-10.6	7.2-9.2	6.4-8.2	8.0-10.2	5.8-7.4	6.3-8.1	3.7-4.7
5-9	8.0-10.8	6.5-8.8	7.3-9.9	7.2-9.8	8.4-11.4	7.3-9.9	6.5-8.8	8.1-11.0	5.9-7.9	6.4-8.7	3.8-5.1
10-14	8.1-11.2	6.6-9.1	7.5-10.3	7.3-10.1	8.5-11.7	7.4-10.2	6.6-9.1	8.2-11.3	5.9-8.2	6.5-9.0	3.9-5.3
15-19	8.6-12.2	7.0-9.9	7.9-11.2	7.8-11.0	9.0-12.8	7.8-11.1	7.0-9.9	8.7-12.3	6.3-8.9	6.9-9.8	4.1-5.7
20-29	9.5-13.2	7.7-10.7	8.7-12.1	8.5-11.9	9.9-13.8	8.6-12.0	7.7-10.7	9.6-13.3	6.9-9.6	7.6-10.6	4.4-6.2
30-39	11.1-14.9	9.0-12.1	10.2-13.7	10.0-13.4	11.6-15.6	10.1-13.5	9.0-12.1	11.2-15.1	8.1-10.9	8.9-12.0	5.2-7.1
40-49	11.8-15.7	9.6-12.8	10.9-14.5	10.7-14.2	12.4-16.5	10.7-14.3	9.6-12.8	11.9-15.9	8.6-11.5	9.5-12.7	5.6-7.1
50-59	12.8-16.7	10.4-13.6	11.8-15.4	11.5-15.1	13.4-17.5	11.6-15.2	10.4-13.6	12.9-16.9	9.4-12.2	10.3-13.5	6.0-7.9
60-69	13.3-17.3	10.8-14.1	12.2-15.9	12.0-15.7	13.9-18.2	12.1-15.8	10.8-14.1	13.4-17.5	9.7-12.7	10.7-14.0	6.3-8.2
70-79	13.7-17.7	11.1-14.4	12.5-16.3	12.3-16.0	14.3-18.6	12.4-16.1	11.1-14.4	13.8-17.9	10.0-13.0	11.0-14.3	6.5-8.3

¹ Data collected by Dr. V. Bergamini.

which 68 per cent of values from normal muscle will lie (concentric electrodes). The ranges of mean duration for different muscles are given for the various age classes (*Buchthal et al.* 1954 c; comp. also *Hertz et al.* 1954). When applying the table it must be taken into account that different electrodes may give different mean durations (*Buchthal et al.* 1954 b). Therefore, mean values from 4 or 5 normal muscles at a given age should be recorded with each batch of new electrodes and compared with the corresponding data of the table.

SUMMARY

Mean action potential durations, amplitudes and shapes are given of various normal muscles for comparison with findings in clinical electromyography.

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TWENTY YEARS OF NEUROSURGERY IN DANMARK

A Short and Most Incomplete Survey

By

EDUARD BUSCH, NIELS JØRGEN KRENCHIEL

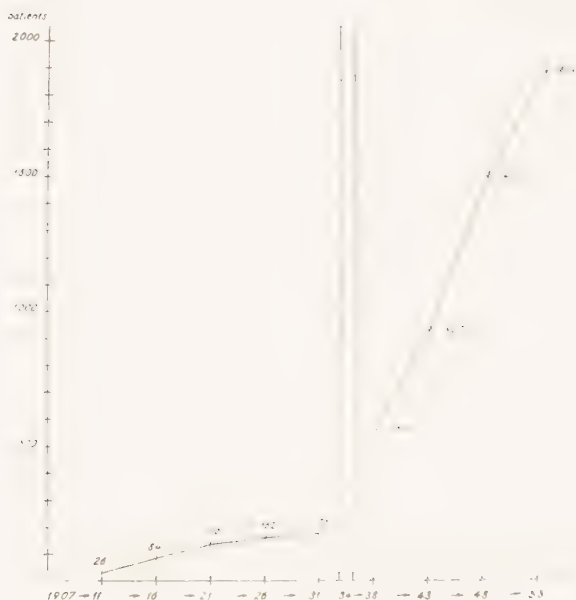
and ERIK KIØRBOE

In 1910 a budding Danish neurologist, 24 years old, visited London and saw the work of Sir Victor Horsley at the National Hospital, Queen's Square. Wistfully he wrote home: "*One thing more. While wandering around the rooms of the National Hospital one easily falls into a beautiful dream: The dream of a similar hospital in Copenhagen*" —a hospital, which "*could be a centre of neurosurgery in Danmark.*"

In 1924 the same neurologist visited America and saw Harvey Cushing. After his return he wrote: "*It would be a beautiful thought, if Danmark, perhaps as the first country in Europe, could establish what the Americans started to introduce ten years ago: A neurosurgical department.*" After asking both general surgeons and neurologists for resignation he explains that the coming neurosurgeon will "*after some time develop from a mere brain-operator into a brain-surgeon. He and his department will increasingly learn to make their own diagnoses and to make their own indications for surgery. Just as appendicitis from a medical has become a surgical malady, so tumors of the brain, of the spinal cord, and many other conditions from neuromedical will become neurosurgical diseases.*"

In 1928 the neurologist, now 43 years old, is somewhat dispirited, but still fighting: He gives up the idea of a municipal department for the city of Copenhagen, because such a department should take patients from all parts of Danmark, and he very much doubts that the University Hospital and the Danish State authorities will realize the plan: "*In reality I see only one chance, viz. a private hospital for brain surgery.*"

In 1931, after the establishment of a neurological department in the University Hospital of Copenhagen, the undaunted man writes: "*If one, as a neurologist, has one burning wish, it is that not only medical*



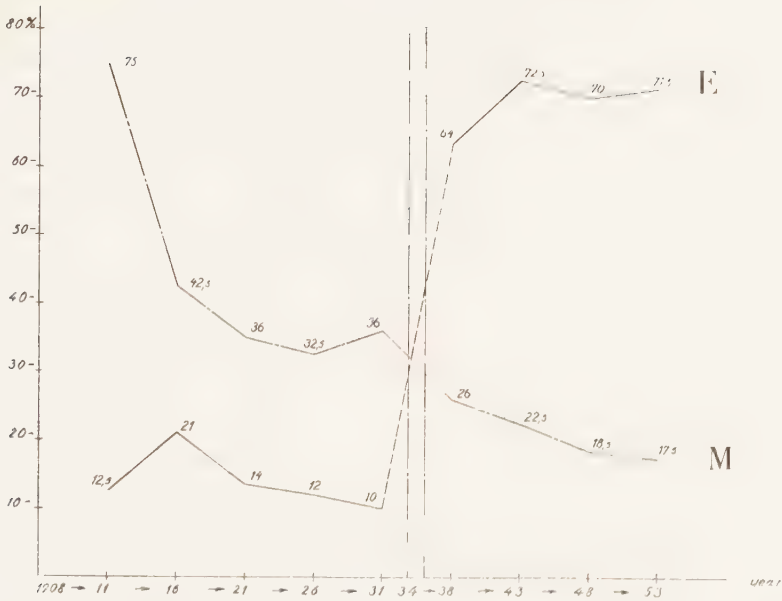
Graph 1.

Number of operations for intracranial tumors in Denmark in the unspecialized period (1907-1931) and in the specialized period (1934-1953).

neurology, but also surgical neurology gets the place in the sun which this specialty—and not less the patients—require.”

Thanks to the nestor of Danish neurology, *Viggo Christiansen*, to the general surgeon *Vilhelm Schaldemose*, who up till then had shouldered most of the heavy work of unspecialized neurosurgery, and to *Johannes Frandsen*, Director of Medical Services of Denmark, a small department for specialized neurosurgery was in 1934 at last established in the University Hospital of Copenhagen. This step was felt to be a very daring and experimental one: There were 11 beds and one operating theatre of 4×4 metres. At most 2-3 operations were expected per month and 500 Danish crowns per month were deemed an ample salary for the neurosurgeon in charge. But the start was made, and the following tables and graphs will make it clear that the fear that the small personnel of the first Danish department of neurosurgery starting out in 1934 should lead a lazy and indolent existence was unwarranted.

Even if the figures quoted here are not too exact—they are mainly taken from the annual reports—spot tests have shown that they are sufficiently exact to give what is desired in this paper—a roughly orientating impression of the work done during the first twenty years, during which the population of Denmark grew from 3.7 to 4.3 millions.



Graph 2.

Mortality (M) in operations for intracranial tumors in Denmark in the unspecialized period (1907-1931) and in the specialized period (1934-1953). E = percentage of "effectivity", i.e. percentage of patients operated who leave the departments alive following total or partial excision of their tumors.

The small department of 1934 gradually expanded and thanks to *Johannes Frandsen* and the university and municipal authorities of Århus and Copenhagen a second department was opened in 1943 at Århus University with *Richard Malmros*, a third one in 1953 in a municipal hospital of Copenhagen, with *Bendt Broager* as chiefs. We thank our former collaborators and present colleagues for the permission to include the figures of their departments in this survey.

The tables and graphs following will mainly speak for themselves and only a few words shall accompany them. The graph showing *intracranial tumors* (Fig. 1) shows the number of such operations performed in Denmark 1907-1931, i.e. in the unspecialized period, and following a short uncharted interval (1932-1933) the number in the specialized period. While operations have been increasingly more radical the *mortality rate* (Fig. 2) is still seen to fall. Still more significant is the *percentage of effectivity* by which we mean the percentage of patients with intracranial tumors which leave the department alive after total or partial removal of their tumors. While this percentage before 1934 was about 10 %, as mainly decompressions were performed, it is now around 70 % (Fig. 2).

TABLE 1
Intracranial tumors in Denmark 1934-1953.

		Gl	Mg	N	A	Cg	Ang	Meta	Var	N-V	Total
	1934...	21	10	2	1	7	0	1	0	4	46
	1935...	48	15	4	7	10	7	3	0	13	107
	1936...	56	16	6	4	7	21	3	0	30	143
	1937...	53	23	5	4	8	15	4	0	8	120
	1938...	50	25	12	11	10	15	4	0	7	134
I	1934-38	228	89	29	27	42	58	15	0	62	550
II	1939-43	382	123	49	53	61	120	62	11	62	922
III	1944-48	600	181	64	110	86	178	93	11	168	1491
	1949...	125	37	14	26	27	30	26	2	36	323
	1950...	129	37	8	18	21	63	33	6	44	359
	1951...	149	33	14	22	12	68	27	3	37	365
	1952...	159	39	12	22	19	54	33	7	51	396
	1953...	156	55	19	19	23	76	37	4	40	429
IV	1949-53	718	201	67	107	102	291	156	22	208	1872
	1934-53	1928	593	209	297	291	647	326	44	500	4835

Gl = Gliomas. *Mg* = Meningiomas. *N* = Neurinomas. *A* = Adenomas.

Cg = Craniopharyngiomas a. o. congenital tumors. *Ang* = Angiomas, aneurysms a. o. vascular malformations. *Meta* = Metastases, sarcomas, granulomas.

Var = Varia. *N-V* = Non-verified tumors.

The figures include operations for recurrences.

The number of tumors in the various groups (Table 1) is seen to increase in all four five-year periods. An analysis, however, makes it clear that the increase during the last period (1949-1953) is partly due to *angiomas, aneurysms a. o. vascular malformations*, which are included here from old and perhaps bad habit. These affections increase in this last five-year period by 63 %, while increase in *meningiomas* is small and the figures for *neurinoma* and *adenoma* are unchanged. The increase in the period 1949-1953 is mainly due to *malignant disease*—the “meta”-group increasing by 68 %, while the increase in gliomas is due to an increase in *glioblastomas*, which now arrive in the neurosurgical departments in time to be verified, if nothing else. Still, it seems that useful relief, if no cure, can be obtained in some of these patients. The increase in *non-verified tumors* is mainly due to inoperable glioblastomas or metastases, verified by angiography only. We may consequently conclude that in the years to come no increase in intracranial tumors is to be expected to be compared with the increase up till now.



Graph 3.

Number of patients admitted to the departments of neurosurgery in Denmark 1934-1953. Below: Number of operated intracranial tumors.

The dramatic increase in *admissions to the neurosurgical departments* (Fig. 3) is also seen not to depend upon intracranial tumors but to be connected with the new fields opened up for neurosurgical therapy in this period (Fig. 4): *Prolapse of the intervertebral disc* and *psychosurgery* were both, very different as they are, taken up in fear and trembling and from a small and cautious beginning grew in frequency as it was realised that neurosurgery in these fields was worth while. In spite of a conservative attitude at least as compared with some countries—*disc surgery* grew explosively and it was a great help when the orthopedic departments began to take up this problem (see Table 3). It is felt that no great reduction in surgical activity is to be expected in this field in the near future and new techniques give hope of still better results.

For *psychosurgery*, however, the figures are certain to fall in the years to come as the reserve of chronically mentally diseased is gradually exhausted. The same is felt to be true of *surgery of the sympathetic system* (Table 3), where the increase is nearly solely due to operations performed in *arterial hypertension*. The various types of sympathectomy performed have admittedly been the only hope for some and of great help to many patients, but we have always felt that surgery in



Graph 4.

Number of various groups of patients admitted to the departments of neurosurgery in Denmark 1934-1953: *Discs* = prolapse of intervertebral discs, ligamentary spinal root compressions, etc. *Traum. B.D.* = Acute and chronic traumatic brain disease, chronic atrophic brain lesions. *Psych.* = Psychosis, neurosis: The rise is entirely due to psychosurgery. *Symp.* = Surgery of the sympathetic system. The rise is almost entirely due to sympathectomies in arterial hypertension.

these conditions was *faute de mieux*—performed as the at the moment best therapy in a time of little or no understanding of the underlying pathophysiology. This may be true of any therapy at any time, but in arterial hypertension, we have now a reasonable hope that new and more adequate therapies will relieve the neurosurgeon of the burden of at least some of these operations.

Another reason for the explosive growth in admissions to neurosurgical departments in Denmark is *traumatic brain lesions* (Fig. 4). The increase in neurosurgical beds made it possible for the neurosurgeons to accede to the demands of the general surgeons to take over these patients in growing numbers and with ever more gratifying results. In the graph are included *chronic traumatic* and *other atrophic*

TABLE 2

Intracranial Surgery—other than tumors—in Denmark 1934–1953.

	AcB.	ChrB.	AcInf.	ChrInf.	Malf.	Art.	Psych.	EpiCef.	Obs.	Total
1934–38	20	123	9	77	32	1	0	7	201	470
1939–43	202	456	109	236	50	79	18	107	293	1550
1944–48	1039	1150	199	437	93	322	889	570	456	5155
1949–53	1404	1155	288	488	208	604	2408	596	475	7626
1934–53	2665	2884	605	1238	383	1006	3315	1280	1425	14801

AcB. = Acute traumatic brain affections. *ChrB.* = Chronic traumatic brain affections & atrophic brain lesions. *AcInf.* = Brain abscess a. o. intracranial acute inflammations. *ChrInf.* = Chronic intracranial inflammations. *Malf.* = Malformations. *Art.* = Arteriosclerosis, thrombosis, etc. *Psych.* = Psychosis, neurosis.

Epi.Cef. = Epilepsy, migraine, etc. *Obs.* = obs. f. intracranial tumor.

brain lesions, but an analysis (Table 2) shows that the increase is mostly due to acute patients. With modern traffic in mind it is to be feared that no decrease, but rather a steady increase in these patients is to be expected in the years to come. While surgery of *peripheral nerves* (Table 3) is stationary, it is felt that the figures of all sorts of *pain surgery* will increase as stereo-tactic and other new methods of treatment are evolved, and work done in the laboratories gives hope of even more adequate, if more complicated methods.

With the promise of a fourth department of neurosurgery in Odense next year it is felt that Denmark at the present time is one of the countries in the world best covered as to neurosurgery, and the problems of the future will mainly be in organisation and completion of the

TABLE 3

Various Forms of Neurosurgery in Denmark 1934–1953.

	SpinT.	Disc.	Ospin.	Periph.	Neural. etc.	Symp.	Var.	Total
1934–38	42	8	55	25	161	12	1	304
1939–43	119	426	246	99	312	100	55	1357
1944–48	175	2433	460	340	1194	984	208	5872
1949–53	182	2577	503	370	1110	1196	262	6947
1934–53	518	5444	1264	834	2777	2292	526	14480

SpinT. = Spinal tumors. *Disc.* = Intervertebral disc prolapse & other spinal root compressions. *Ospin.* = Other spinal affections. *Periph.* = Peripheral nerves. *Neural, etc.* = Neuralgias, spasms, pain surgery. *Symp.* = Surgery of the sympathetic system. *Var.* = Varia.

The increase in operations for intervertebral disc prolapse is still more striking: In the years 1944–48 and 1949–53 the various orthopedic departments in Denmark admitted 78 and 747 patients, respectively. These patients are not included in the above.

staffs of the departments. The work of neurosurgery is a heavy one, and at least two, perhaps three, fully competent neurosurgeons should be available in each centre. On the other hand it must be realised that a neurosurgical department should not be too small, as uncommon lesions then will become *too* uncommon—experience deficient and results deteriorate.

However—inexact and incomplete as the figures and words here presented are felt to be, they seem fully to vindicate the introduction of specialized neurosurgery in this country and—even if other persons and other factors were decisive in establishing and developing the first small beginning of Danish neurosurgery—it does not seem inappropriate that this short survey of the first twenty years should appear in a volume honouring *Knud Krabbe*—the young neurologist of 1910 and his beautiful dream.

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A CASE OF SCHILDER'S DISEASE IN AN ADULT WITH REMARKS TO THE ETIOLOGY AND PATHOGENESIS

By

ERNA CHRISTENSEN and MOGENS FOG

Schilder's disease belongs to the demyelinating diseases and is characterized by subcortical demyelination, axonal degeneration, and different sorts of glial proliferation. Numerous types and varieties have been described under a long list of names: Schilder's encephalitis periaxialis diffusa, centrolobar sclerosis, encephalo-leucopathia scleroticans, progressive degenerating subcortical encephalopathy, leuco-encephalopathia myeloclastica primitiva, leucoencephalopathia periaxialis diffusa concentrica, etc. Krabbe's name is intimately connected with this disease as in 1916 he described the acute familial form in infants.

This group of diseases can be divided into acute, subacute, and chronic forms—and both sporadic and familial forms are seen. They can be classified according to heredity and clinical course or according to morbid anatomy and pathogenesis.

Classification according to heredity and clinical course:

A. *Familial cases:*

1. The familial acute form in young infants (*Krabbe* 1916) (12).
2. The infantile chronic familial form: Pelizaus-Merzbacher's disease or leucoencephalopathia periaxialis diffusa (*Merzbacher* 1910) (13).
3. The familial juvenile chronic forms described by *Scholz* (19).
4. The familial chronic form in adult persons (*Ferraro*) (8).

B. *Sporadic cases:*

These are commoner than the familial cases and may also present acute, subacute forms (Schilder's disease (18), Balo's disease (2)), or

a more chronic course with specification in infantile, juvenile, and adult types.

Classification on the basis of both morbid anatomy, pathogenesis, and heredity has been attempted among others by the Danish authors *Einarson* and *Neel* (6-7) in three monographs. They have set up the following classification:

1. The glioblastomatous type or leucencephalopathia glioblastomatosa characterized by big blastomatous—often multinucleated—cells of astrocytic origin with very distinct but irregular nuclei.
2. The exogenous inflammatory reactive type or Schilder's disease.
3. The non-familial sporadic degenerative types:
 - a. with large numbers of macrophages filled with fat,
 - b. with metachromatically stained basophil material.
 This last variant is very rare, and the authors never found an adult case.
4. The heredo-degenerative familial types.
5. Encephalitis periaxialis concentrica (*Balo*) (2).

Greenfield (10) proposes the following pathological classification:

1. *The inflammatory reactive type* (familial or not familial) without any sharp dividing line between the inflammatory reactive type of diffuse cerebral sclerosis of *Einarson & Neel* and cases of subacute demyelinating encephalopathy and myelopathy which can be classified as disseminated sclerosis, diffuse myelitis, and neuromyelitis optica.
2. *The metachromatic degenerative type*. This may be familial and gives evidence of being a general disorder of lipid metabolism in the brain, the liver, and other organs of the body.
3. *Another familial type*, which also may be a disorder of lipid metabolism with packets of epitheloid and globoid cells.

Greenfield criticizes the grouping of familial cases by age at onset and rate of progress as well as the blastomatous cases, but he concludes that neither the number of observations of these rare forms of diffuse sclerosis nor the completeness with which they have been recorded suffices to determine whether or to what extent there exist transitional forms between the groups.

Russell (16), *Adams* and *Kubik* (1) also classify the demyelinating diseases according to their morbid anatomy. Like *Greenfield* they regard multiple sclerosis and diffuse sclerosis from the same point of view.

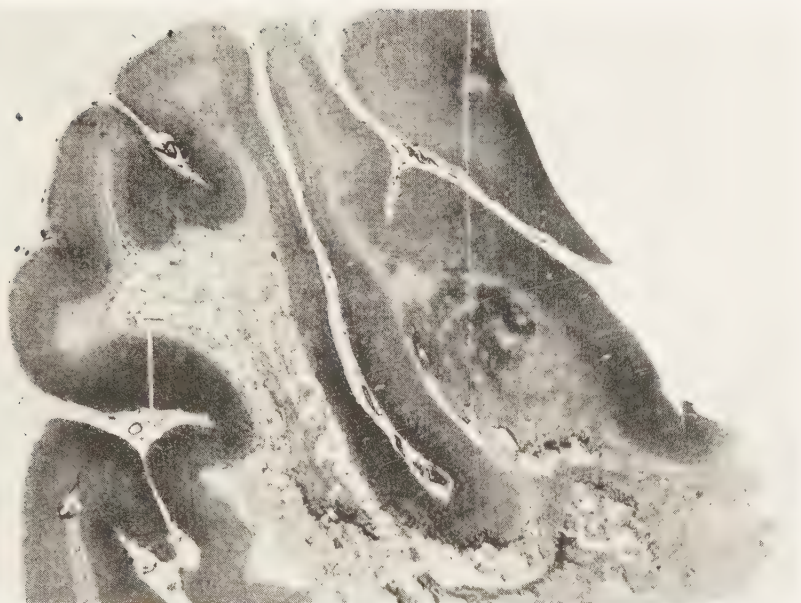


Fig. 1.

Right occipital lobe around the calcarine fissure with damage of the white matter except the arcuate subcortical fibres.

Mallory's P.H.A.-stain, Magnification 4 $\times$.

Adams and Kubik propose the following classification:

- A. Multiple sclerosis.
 1. Chronic relapsing encephalomyelopathic form.
 2. Acute multiple sclerosis.
- B. Acute disseminated encephalomyelitis.
 1. Measles, smallpox, chickenpox, mumps, and "influenzal" encephalomyelitis.
 2. Rabies vaccine and smallpox vaccine encephalomyelitis.
- C. Cerebral sclerosis of the demyelinating type.
 1. Schilder's encephalitis periaxialis diffusa.
 2. Metachromatic leucoencephalopathy.
- D. Acute and subacute necrotizing hemorrhagic encephalomyelopathy.
 1. Acute encephalopathic form.
 2. Acute and subacute necrotic myelopathy.

Russell concludes that in the present state of our knowledge little seems to be gained by the subdivision of these different manifestations of diffuse cerebral demyelination.

The etiology is still obscure; different factors have been considered.

- I. *Exogenous factors.* The possibility of a specific virus infection



Fig. 2.
Premotor cortex with well preserved nerve cells.
Bielschowsky stain. Magnification 285 $\times$.

has been discussed in connection with the etiology of demyelinating diseases of the cerebral nervous system.

Other hypotheses have been advanced such as allergy and tissue-sensitisation in the postvaccinal type of encephalitis and experimental disseminated encephalomyelitis following repeated injections of heterologous brain emulsions (*Ferraro & Jervis*) (9).

A special form of diffuse sclerosis, the so-called "Swayback" disease in newborn lambs, where deficiency of copper seems to be the cause, may be mentioned (11). Also anoxia, especially the histiotoxic type seen after intoxications with potassium cyanide, may give demyelination in the white matter.

Other exogenous factors to be considered are dietetic deficiency, traumatic injuries, and lues.

II. *Endogenous factors.* Both familial heredity and constitutional factors may be of importance.

It seems probable that different etiological factors may be combined in a single case and then represent different links in the pathogenetic complexity of this disease, which also is still obscure.

Several authors have noticed the disappearance of the interfascicular oligodendroglia cells in demyelinating areas in diffuse sclerosis, and in 1928 *Rio Hortega* advanced the tentative hypothesis that the

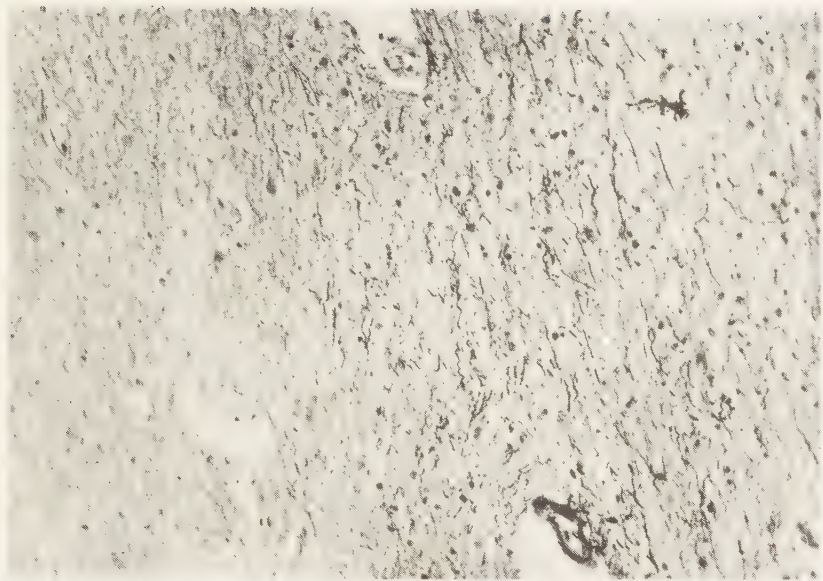


Fig. 3.

Temporal lobe. Border line between normal and degenerative white matter.
Davenport neurofibril stain. Magnification 285 $\times$.

oligodendroglia might play a significant role in the nutrition of the myelin sheaths or in the formation of myelin. Therefore damaging of this element would lead to demyelination and be the primary lesion in these diseases. Among others *van Boegart & de Wulf* (3), *Einarson & Neel* (6-7), *Russell* (16), *Brain & Greenfield* (4), and *Adams & Kubik* (1) have drawn attention to the dyscatabolic factor in the metachromatic type of leucoencephalopathy containing granular metachromatically stained bodies instead of granules of neutral fat and cholesterol esters which are ordinarily products of myelin degeneration. *Greenfield* (10) in his case found simultaneous presence of the metachromatic material in the Kupffer cells of the liver and in the collection tubules of the kidney.

Pathology: Macroscopical and microscopical examination of the brain gives a varying picture according to the severity, the special sort of degeneration, and the influence of the time factor, which is characterized by the varying degree of gliosis or softening and discolouring of the affected areas, but the dominating picture is symmetrical degeneration of the white matter especially in the occipital lobes, eventually spreading forward to the frontal and temporal lobes. Exceptions to this distribution of the pathological process occur. The white matter of the cerebellum may show the same changes as found in the cerebral



Fig. 4.

White matter below the calcarine fissure. Complete destruction of myelin sheaths. oligodendroglial cells also on the border line, where numerous monstrous astrocytes are seen.

Mallory's P.H.A.-stain. Magnification 150 $\times$.

hemispheres. The colour of the affected areas which are sharply demarcated from the normal tissue varies from greyish-red to yellow-brown. The consistence may be fibrous or hard, spongy or gelatinous.

Microscopic findings: The outstanding histological feature consists of a complete loss of myelin sheaths within the affected areas, but the destruction usually stops sharply below the subcortical arcuate fibres. In early stages the affected areas are perivascularly localized. In areas with total destruction of the myelin the axis cylinders are also damaged.

The neuroglial reactions differ from case to case depending upon the time factor and the severity of the process. The interfascicular oligodendroglial cells are first affected. They often show swelling and increase in cytoplasm. The astrocytes proliferate and hypertrophic forms—the so-called monster-cells—are very common phenomena.

In old cases the fibrillary glial network also proliferates. The microglial cells act as phagocytes. They contain fat globules and myelin debris or, as mentioned above, metachromatically stained granular bodies.

Clinical symptoms are linked with the age of the patient.

In children: Frequent symptoms are considerable change in mental reactions, spastic paralysis, and epileptic seizures, while visual disorders are seldom found.

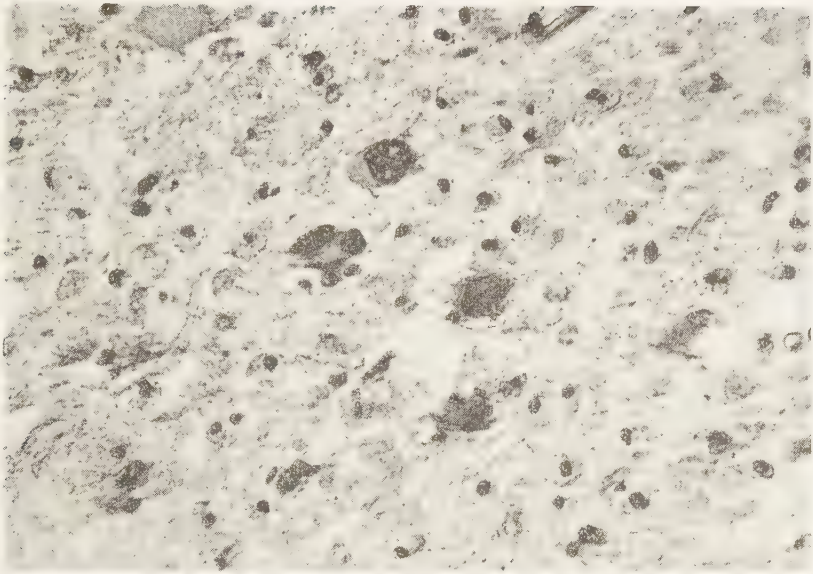


Fig. 5.

Multinucleated monstrous astrocytes between amoeboid microglial cells in degenerated white matter.

Hematoxylin-eosin-stain. Magnification 285 $\times$.

Among adults progressive disturbances of vision is an early and very frequent symptom; also impairment of mental faculties with deterioration may occur early in the disease. Different types of aphasia, apraxia, and Jacksonian fits are very common symptoms.

It is a rare disease which mostly attacks children and young persons—only a few cases have been reported in adults—and very few in middle age.

Greenfield emphasizes that until we know more about the cerebral diffuse sclerosis it is important that all unusual cases are reported. This is the justification for publishing the following case.

Case record. 964/1953. Male, born 8.4.1894, died 3.12.1953. The patient was a labourer under the Road Board. He had for 24 years worked with concrete cover of the roads.

Family history: No history of disease in the family.

History of the patient: For many years periodical headache localized to the frontal and temporal regions. When 48 years old he had symptoms of protruded lumbar disc for about three years. Otherwise he was quite well until 2 months before admission to hospital.

From that time he had progressing difficulties in writing and reading. He could not remember how to write the words—only single letters.

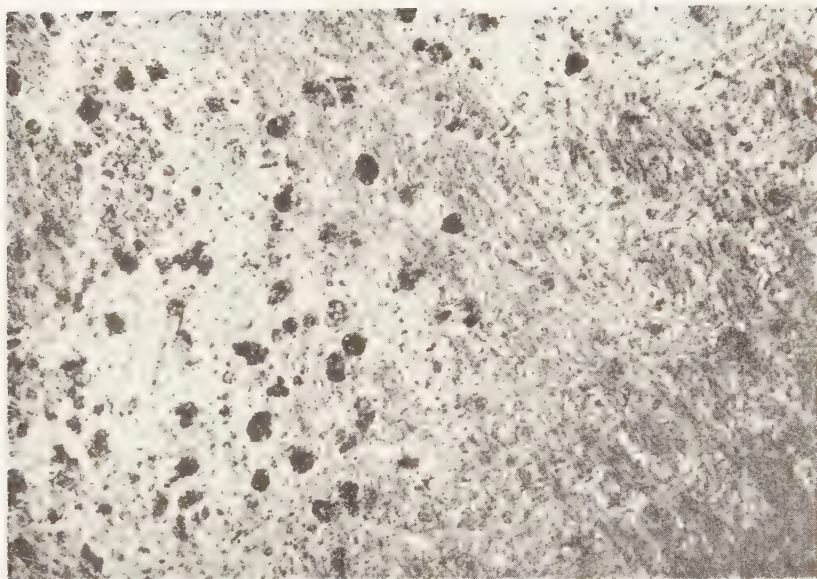


Fig. 6.

Amoeboid microglial cells containing fat.
Scarlet-red stain. Magnification 150 $\times$.

and he could not recognize written and printed matter even if he was able to see the single letters.

Gradually disorders of vision developed, especially in the right part of the visual field, and an examination on 24th July 1953 revealed a right-sided homonymous hemianopsia.

On admission to the Neuro-Medical University Clinic on 18th September 1953 he also complained of pains in the left cheek. On examination he looked much older than his age; he was dull, forgetful, and there was a moderate degree of expressive aphasia, marked bilateral reduction of vision, now without hemianopsia. The light reaction of pupils was weak. The eye grounds were completely normal, but the patient behaved as a blind person. Examination of ears revealed presbycusis and nystagmoid movements of a type indicating a cerebral lesion. There was also a slight central paresis of the left facial nerve.

Otherwise the neurological examination was normal, but over both lungs there was bronchial respiration and the liver and spleen were enlarged. No edema could be found.

X-ray of the lungs showed many small calcified lesions in both lungs, in the hilus glands, and more indistinct confluent fresh infiltrates of the central parts of both lungs.

Wassermann reaction and differential counting of the blood, histo-



Fig. 7.

Polypous prolongations of abnormal tissue into the normal parts of the white matter in the frontal lobe.

Mallory's P.H.A.-stain. Magnification 25 $\times$.

logical examination of the sternal marrow revealed nothing abnormal. In the cerebrospinal fluid there was a slight rise in the protein content, but the number of cells was normal. The sedimentation rate was also normal, and the tuberculin reaction (Mantoux) was negative.

The conclusion was drawn that the infiltrate in the lungs, the enlargement of liver and spleen must belong to the same systemic disease which also caused the cerebral disorder, and the diagnosis: sarcoidosis (lymphogranulomatosis benigna) was considered probable. He was therefore treated with A.C.T.H. for 14 days. During this time his mental symptoms progressed, he grew paraphasic, nearly aphasic, disoriented, confused, and negativistic.

As an intracranial space-filling process was now suspected, air-encephalography was performed. The ventricular system was moderately dilated on both sides and there was plenty of air on the base of the skull.

E-E-G- revealed diffuse moderate dysrhythmics.

During the stay in the Neurological Clinic he grew more and more noisy, anxious, and agitated, and was transferred to the Psychiatric Clinic on October 30, 1953, where his symptoms aggravated, he grew totally blind and quite aphasic, could only produce some unintelligible

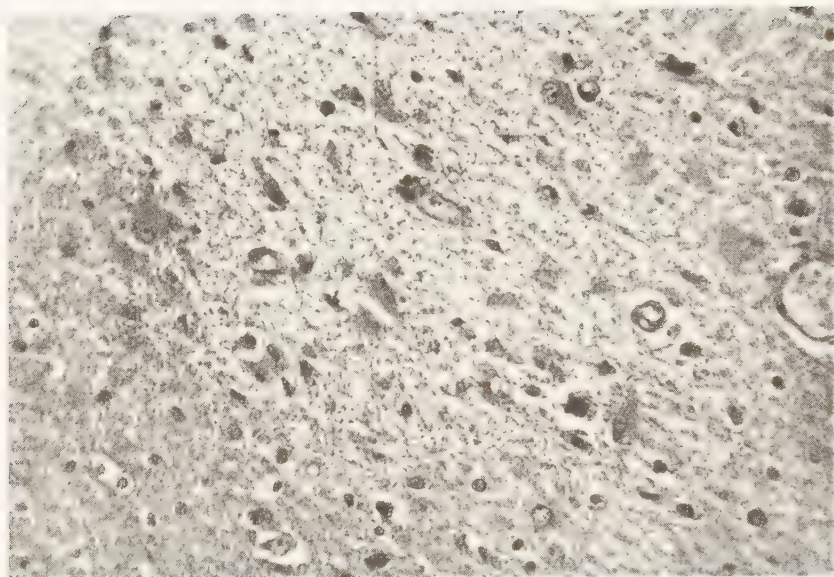


Fig. 8.

Degenerative area with degeneration of oligodendroglial cells on the border line.
Mallory's P.H.A.-stain. Magnification 285 $\times$.

sounds. There was periodic agitation and a rapidly progressive dementia.

The left-sided facial palsy increased and both plantar reflexes were extensor. The last days of his life he was comatous and died in hyperthermia on December 3rd, 1953.

Necropsy: The paratracheal *lymph-nodes* were enlarged, fibrous and calcified.

Both *lungs* revealed very progressive alterations, especially about the hilus, where the tissue was of a very hard consistence. The cut surfaces were fibrous, marmorated, of a bluish colour, with numerous calcified nodules of varying size.

The *liver* was enlarged ($27 \times 10 \times 9$ cm), smooth, and solid of consistence.

The *spleen* was also enlarged, with numerous small nodules, while the tissue itself was very soft as in inflammatory processes.

Histological examination of the *lymph-nodes* revealed complete obliteration of the normal structure, with fibrous, hyalinized, whorled areas and granulomas, surrounded by thin hyalinized streaks and calcifications, as in sarcoidosis.

The *lungs* presented fibrous, whorled, hyalinized areas, in some of which were antracotic deposits and/or granulomas with big bright cells

and lymphocytic infiltration. Giant cells containing Schaumann's bodies and asteroid bodies were also found, but nowhere caseous necrosis.

In the *spleen* were seen strange hyalinized connective tissue nodules with calcifications surrounded by hyperemic hemorrhagic tissue from the spleen.

Examination of the *liver* only revealed periportal lymphocytic infiltration and cadaverotic alterations. Frozen sections and fat staining were not carried out on the liver tissue.

Diagnosis: Sarcoidosis (lymphogranulomatosis benigna) in lungs, spleen, kidneys, and lymph-nodes.

Examination of the brain: The cerebral convolutions were normal, the subarachnoidal space contained an excess of cerebrospinal fluid, the leptomeninges, the dura, and the base of the skull were normal.

After fixation the brain weighed 1520 gm. On coronal sections the white matter looked soft, friable, and greyish-yellow in the posterior half of both hemispheres including the external capsule and the island of Reil, the white substance in both temporal lobes and the callosal body. Demarcation between the cortex and the white matter was sharp (fig. 1). The basal ganglia, mesencephalon, pons, medulla, cerebellum, and spinal cord revealed nothing macroscopically abnormal.

Microscopic examination. In the cortex the ganglion cells were chromophobic, but otherwise normal without satellitosis (fig. 2).

The white matter from the posterior half of both hemispheres showed complete demyelination, destruction of the neurofibrils (fig. 3), disappearance of the interfascicular oligodendroglia (fig. 4), numerous monstrous, singularly multinucleated, some fibrillary astrocytes (fig. 5), and finally masses of amoeboid microglial cells containing lipoid (fig. 6). Scattered perivascular lymphocytic infiltrations were present, otherwise the vessels were normal except for perivascular cuffs of microglial cells in the adventitia. An unusual feature was the numerous monstrous protoplasmatic astrocytes with peripherally placed big nuclei in the degenerative areas.

On the boundary between the normal and abnormal white matter in the middle of the brain the histological examination revealed polypous prolongations of abnormal tissue into the normal parts of the white matter in the frontal lobes (fig. 7). In some of the patchy degenerative areas the myelin was still preserved while the oligodendroglial cells were degenerated and in the periphery plenty of monstrous astrocytes were present (fig. 8). The histological picture with the patchy degeneration was here similar to the picture of multiple sclerosis. Around the occipital horns the demyelination could be followed right to the ependyma of the ventricular wall, but the ependymal

cells were normal. In the posterior parts of the brain where the destruction was most pronounced cystic degeneration occurred in the white matter.

The subcortical arcuate fibres in the white matter were undamaged also in these areas.

The degenerative white matter has been examined for metachromasia with different methods. Weigert's mucicarmin-stain on paraffin-sections gave a negative result. Toluidinblue-stain on frozen sections also gave a negative result. P.A.S. (periodic acid Schiff reaction) stain established the occurrence of red granulas both in microglial cells and in the monstrous astrocytes. According to *Pearce* (15) five substances may be expected to give positive results in paraffin sections: polysaccharides, mucopolysaccharides, mucoproteins, glucoproteins, and glucolipoids.

DISCUSSION

The unusual features and interesting facts in this case are:

(1) The age of the patient, (2) the very fast progression of the disease, (3) the simultaneous presence of sarcoidosis in other organs of the body, (4) the predominance of monstrous, often multinucleated astrocytes in the degenerative areas, (5) the primary damaging of the oligodendroglia cells before complete demyelination in fresh degenerative zones, and (6) the tendency towards perivascular arrangement of these zones.

As for the age our patient seems to be the oldest with Schilder's disease reported in the literature. The difficulty in making the diagnosis from a clinical point of view appears from *Meyer, Leigh* and *Bagg's* publication (14): A rare senile dementia associated with cortical blindness, with three case records identical with our case. The patients were all men between 35-55 years old. The disease developed after influenza in one case and "spontaneously" in the other two cases. They all died four to six months after the onset of the symptoms. The histological examination revealed changes in the cerebral cortex, most marked in the occipital lobe including the calcarine region, and only in one case there were demyelination and damage to the axis cylinders.

The very acute and fatal course of the disease in our case renders both an intoxication and an allergic reaction a reasonable explanation.

When the clinical diagnosis of sarcoidosis in the other organs was made, he was treated with A.C.T.H. and from that time there was a

very rapid progression of his brain disease, but it is impossible to decide whether this is more than a coincidence.

The hypothesis of an intoxication from his sarcoidosis must be considered, but several authors (*Teilum*) (20) regards this disease as an allergic reaction in the reticulo-endothelial system; therefore it is also natural to suppose that both lesions (sarcoidosis and Schilder's disease) are coordinate allergic reactions, but the etiology remains obscure in our case.

From a histological point of view it is natural to consider the brain damage in our case as allergic -as an Arthus phenomenon, which in other organs is characterized by local necrosis and inflammation. Experimental allergic brain lesions (*Ferraro*) (9) are characterized by dilatation of the vessels, perivascular sloughing of tissue or necrosis, and microglial phagocytic reaction; according to this we find perivascular damaging or disappearance of the oligodendroglial cells and very slight degenerating of the myelin sheaths in the most recent lesions. The destruction of the oligodendroglia and the presence of the swollen astrocytes also suggests an intoxication, but exclude an infection and identify the pathological process as a degeneration. This conclusion is drawn by *Russell* and *Tallerman* (17) about the familial form of progressive diffuse cerebral sclerosis, and they call attention to the histological similarity between the familial and the sporadic cases of diffuse sclerosis and the Swayback disease in lamb.

The primary damaging of the oligodendroglial cells supports *Hortega's* hypothesis that myelin sheaths are nourished from these cells. (5).

We regard the findings of numerous monstrous astrocytes as a response to the degenerative phenomenon and not as a glioblastomatous form as considered by *Neel* and *Einarson*. Primary in the lesion is in our opinion the degeneration of oligodendroglial cells in the white matter with secondary damage to the myelin sheaths.

SUMMARY

A 59-years old, previously healthy labourer in a few months develops a fatal disorder with progressive reduction of vision and mental deterioration. The examination reveals symptoms of sarcoidosis, which is verified by the p.m. histological examination of lungs, lymph-nodes, spleen, and kidney. The cerebral disorder is diffuse sclerosis. Considerations of the etiology and pathogenesis of Schilder's disease and the relation between this disease and sarcoidosis are proposed.

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THE IDEA OF A PRESENCE

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The purpose of this article is to describe a rather unusual mental experience which may occur in some psychotics; rarely in epileptics as an aura and even in normal persons in certain circumstances. Scarcely any clear-cut account of this phenomenon exists in neuro-psychiatric writings, in the English language at any rate, though it has been alluded to in the literature of divinity and of occultism. Almost alone among psychiatrists, Jaspers (1913) has given an adequate description. Certainly it finds a place in fiction, but this fact is not necessarily a disadvantage, for, as Dupré used to teach . . . "*voulez-vous pénétrer les secrets de la psychiatrie? Lisez les poètes et les romanciers.*" The phenomenon in question comprises a feeling, or an impression—sometimes amounting to a veritable delusion—that the person concerned is "not alone". Or, if it should be that he is actually in the company of others, that there is also some other being present, when really this is not so. The experience is often a vague one, intangible and elusive, for the visitant can neither be seen, heard, nor felt. In other words the phenomenon is an extracampine one, to employ the terminology used by Bleuler.

Sometimes the idea is vivid; sometimes it is subtle and ephemeral. In duration it may be either sustained or transient. Or, yet again, it may repeatedly come and go, wax and wane. The identity of the visitant or "presence" is but rarely established. Usually the feeling merely entails the belief that there is "someone" in the vicinity. Or, the impression may not amount to anything more than an intangible feeling "as if" one were not alone. The "someone" in question may have either a beneficent or a sinister quality—either protective or menacing. At other times there is no emotional accompaniment: the visitant in

these cases is neutral, colourless and devoid of personal significance (though realisation of the fallaciousness of the belief may engender its own emotions of awe, wonder, bewilderment or fear).

This "idea of a presence" may be illustrated by a couple of examples which came to one's notice while serving with the Royal Navy during the war.

A sailor, whose ship had been torpedoed, was adrift in a life-boat with a few other ratings. Rations were minimal, consisting of a biscuit and a few ounces of water a day for each man. No protection existed against the cold and the wet, and as the frail craft was tossed about on the mountainous seas, hopes of survival vanished. Indeed the actuarial chances of being rescued were very slender. As physical exhaustion and mental distress increased, the sensorium of the shipwrecked sailors became more and more cloudy. My patient now began to experience a curious phenomenon. There kept recurring in his mind the notion that immediately astern of the life-boat a rescue-vessel was under way, with boom lowered, ready to pick up survivors. Each time this idea arose, he would eagerly look around and scan the ocean, but time and again his hopes were shattered, for no trace of any vessel actually existed.

This was the first instance which came to my attention, and it was as a matter of fact, atypical in that the "presence" entailed not a person but an inanimate object, namely a rescue-ship. The sailor, be it noted, was not alone at the time. He was one of a little band of survivors, and hence he formed a unit within a small and isolated community, which itself could be regarded as very much "alone". Whether other shipmates of his also experienced this idea of a presence—similar or dissimilar in type—is not known. Because of the great suggestibility of members of a shipwrecked community and their tendency towards mass hallucinosis and mass confabulation, we need not be astonished if his idea of a presence was not also shared.

Shortly after this particular rating had been interviewed, another shipwreck-survivor was met with who also had suffered a comparable mental experience. A Fleet Air Arm pilot, who had crashed into the sea during the *Bismarck* action, described to me how he and his observer, while adrift in a rubber dinghy, kept imagining that there was a third person along with them.

Here again the circumstances were comparable. Severe physical discomfort had been present, going on to utter collapse. There had been exposure to bitter cold and wet; and intense thirst and lack of food had led to a dangerous degree of dehydration and of inanition. Prospects of rescue were remote, and though from time to time hopes

would soar in an extravagant and unwarranted fashion, they would soon be dashed again with realisation of the tragic plight.

In a recent account of a raft which was adrift for weeks in the Straits of Malacca, two men—a Swede and a Finn—were involved. The former was attacked and devoured by sharks. The other sailor, who was eventually rescued, afterwards wrote "... for the whole voyage I'd had the strange feeling that someone else was with me, watching over me, and keeping me safe from harm. ... It was as if there were sometimes three people on the raft, not two. With Ericsson dead I felt it more strongly than ever." (Tiira, "Raft of Despair", 1954).

A similar mental phenomenon has also been recorded among Antarctic explorers, as for example in the case of Shackleton and his companion. After struggling across the island of South Georgia against the hazards of a violent blizzard, they eventually reached the shelter and fellowship of their base camp. Recalling this adventure Shackleton said, "I had a curious feeling on the march that there was another person with us." It intrigues us to learn that at this point his comrade interpolated that he too had been aware of some similar experience, but that he had hitherto hesitated to mention the fact.

When discussing this phenomenon as involving normal persons exposed to severe peril, privation or exhaustion, I have occasionally been told of other similar cases. It has been described to me in mountaineers immobilized by bad weather at great heights, as well as in prisoners on a cruel march from one German concentration camp to another. An explorer scaling Mount Everest developed this same trick of the imagination, probably from anoxia rather than exhaustion. During his solitary voyage around the world in a tiny sailing vessel, Slocum at times had the fancy that he had a companion with him.

Something akin may also occur in association with organic neurological states. Being purely subjective experiences they are not always conspicuous. The patient may be reluctant to volunteer the information: the neurologist in his ignorance may neglect to enquire for it, or to record it if mentioned. Consequently we are apt to regard it as a rare phenomenon, though perhaps unjustifiably so.

Thus an epileptic may develop the idea of a presence as part of the aura. A number of examples may be given:

(a) An epileptic woman of 24 had had fits for seven years. Before each of her attacks she used to get a horrible frightening feeling that someone (or something) was behind her, and was pushing her forwards.

(b) An epileptic female of 72 years was prone to curious, transient attacks of compulsive immobility with loss of vision to the right side. Her right hand would

then seem to her to swell to twice its size and to appear "ugly and spiteful". This illusion might continue for hours. At these times she might also have an intangible sensation as if someone sinister ("a bad spirit") were standing behind her left shoulder.

In the next case an hallucinatory element was also present of a primitive kind. By acting as a *point de repère* it was elaborated by the patient into a quasi-delusional state.

(c) A boy of 15 was taking coffee in an open-air café. He suddenly imagined he saw something glistening far over to his right. His mind immediately leapt to the conclusion that someone was standing behind him and to the right, trying to hypnotise him by shining a light into his eyes. In alarm he turned his head and eyes to the right, and then lost consciousness.

In this next case, for which I am indebted to Professor P. C. P. Cloake, it is uncertain whether the phenomenon was hallucinatory or not.

(d) A male epileptic of 26 who had suffered from fits for ten years, developed a terrifying idea that an unfamiliar and unprepossessing face was lurking behind his right shoulder. At times his head felt swollen to twice its size. There were clinical and encephalographic data to show that in this patient the epilepsy was symptomatic of some progressive but chronic diffuse encephalitic process.

In cases like these, the epileptic patient, believing that someone stands in the rear, may turn the head and body in an effort to bring the being into view, and then almost immediately he falls unconscious. Perhaps some of the common cases of versive (or adversive) epilepsy really belong here, the preliminary turning movements being not so much an involuntary rotation as a willed and purposeful act of inspection.

The idea of a presence may also occur as a symptom in narcoleptics, especially during the stage of predormital unease. Hypnagogic hallucinations are apt to appear to such patients, but as a preliminary to these, there may be a brief period of quasi-hallucinoses, where the presence of an intruder in the room is imagined intellectually rather than perceived as a sense-datum. The following case-report illustrates this point. M.H., a female narcoleptic patient, was a victim of very disturbed sleep at night-time. She might wake in the night with such a vivid impression that some intruder was in her room that she would switch on the light. In her more elaborate interdormital delirious episodes she would be hallucinated, especially in the tactile and auditory spheres.

It may be that the third narcoleptic described by Russell Brain (1939) was also a victim of this idea of a presence, occurring during the night, though the possibility of actual hallucinations cannot be excluded. The patient at times would wake in the darkness to find himself out of bed and in a state of fear, believing that someone was in the room creeping towards him. In his panic he would scream: twice he broke windows, and once he kicked a hole in the door.

Among the vague and curious anomalies of corporeal awareness (or body-image) occurring with lesions of the subordinate parietal lobe, an idea of a "presence" may intrude.

A patient seen by Hoff and Engerth (1929) showed a left-sided hemiparesis and a hemianopia. The patient declared that the left half of the body did not belong to him. Sometimes while walking he got the notion that behind him and to his left he was being followed by someone, namely his double. Whenever this idea developed he would lose the feeling of strangeness which affected the left half of his body.

A well-known poet told me that during a childhood illness he developed a curious feeling as if someone (actually a mere acquaintance) had entered his body. Thus he became a composite being with this other person sharing his pains and discomfort. This impression lasted some days and so vivid was it that he naturally believed that the doctors and nurses in attendance knew all about it too.

Here we have a modification of the idea of a presence, the visitant taking up a position not in an extrapersonal spatial relationship, but within the subject's own body. In some ways this forms an antithesis of depersonalization. This patient of course had no parietal lesion. Some other cases are even more complicated in character. A man of 53 with temporal lobe epilepsy (kindly shown me by Dr. Denis Williams) on one occasion sustained an attack which was preceded by the curious notion that his bodily self had grown to one and one-sixteenth of its original size. So vivid was this belief that he was in great fear in case his personality should permanently enter the sixteenth fraction and then separate from the remainder. He could hear himself exclaiming: "Yes, please; yes, please . . ."

Zillig's patient (suffering from parietal injury) developed a fantastic confusional state in which he believed that he consisted of nothing but a head and neck severed from the rest of the body. He imagined he lay in a basket, as a torn-off head among a ghastly collection of other such heads. Outside the basket, decapitated men walked back and forth. This belief was not based upon any hallucinatory experience, but was a sort of dream-state of great complexity (1940).

Elsewhere I have reported the case of a woman with biparietal

atrophy who, among numerous other symptoms, would often wake in the night with a trenchant feeling that someone was in the room—a person whom she knew very well indeed. Sometimes it would dawn upon her that this visitant was none other than herself. The *alter ego* seemed always to be located out of sight, behind her and to her left. So poignant at times was this feeling that she might be impelled to get out of bed and go on tiptoe from room to room with the object of surprising this interloper.

One cannot wonder because neurological patients whose sensorium is clear should be reluctant to confess to such bizarre and macabre experiences. This intangible feeling perhaps amounting to a firm belief, but subsequently proving to be erroneous or delusional, is so unexpected, incongruous and uncanny, as to disturb the victim. Like the amputee and his phantom limb, he may well prefer not to mention it.

The idea of a presence is all the more upsetting to the layman for it is a theme has been not infrequently touched upon by poets and by romantic writers. The conception of the haunted malefactor is not far removed. As an example of literary allusions belonging more or less to this category we may mention T. S. Eliot's "The Waste Land"¹. It has been mentioned by Flaubert ("... He has the feeling that some monstrosity is floating around him—the horror of a crime about to be perpetuated"—"Temptation of Saint Anthony"); by Maupassant ("The Horla"); by H. G. Wells ("... I woke with a start, and with an odd fancy that some greyish animal had just rushed out of the chamber"—"The Time Machine"); and by Denis Wheatley ("The Haunting of Toby Jug").

The symptom accordingly possesses only too often an unsavoury connotation, particularly when the unseen presence seems to threaten rather than sustain. But this is not always the case. There is a weighty theological tradition, if not a literature, too, which implies a protective companionship, the conception indeed of a guardian angel. Thus in Roman Catholic communities the notion of an *angelo custode* is a common teaching and is depicted in religious art as an angel with a wide wingspan standing as an unseen protector behind a little child.

¹ "Who is the third who walks always beside you?
When I count there are only you and I together,
But when I look ahead up the white road
There is always another one walking beside you,
Gliding wrapt in a brown mantle, hooded
I do not know whether a man or a woman
—But who is that on the other side of you?"

A special prayer illustrates this belief:—"Angele Dei, qui custos es mei, me tibi committam pietate superna, hodie illumina custodi rege et guberna."

In similar vein, Satan may at times be depicted in symbolic form crouching beneath the feet of the child. But in Muslim doctrine, the good angel stands behind the right shoulder while the devil is behind the left (hence the superstition of the left hand as being unclean, unlucky, sinister and not "right").

It is not surprising therefore to find that a supernatural or theistic interpretation is adduced by the religious as the obvious explanation of the idea of a presence, especially in the case of distressed and exhausted shipwrecked seamen. The "Guardian Angel" motif is inescapable to those with strong beliefs. As Tiira said of his experiences while adrift, "... perhaps it was my mother's prayers for me in Finland. She was always anxious for my safety. Maybe this strong bond between us came to my mental rescue at this time."

How far is this phenomenon a commonplace among normal children? Doubtless it occurs with greater frequency than is often realized. Something comparable may lie behind the "invisible playmates" theme of the lonely child, the orphan or the evacuee; or those who are homeless, unwanted, or hungry for sympathy and love. In states of putative danger, or illness, or in uneasy solitude, the idea of a presence may be particularly vivid, and may be confidently associated by the child with its belief in a celestial protecting agency or companion.

Similar affective factors may also be mirrored in adults in whom a deep love and understanding forms a strong though inangible bond. Though actually separated, they may seem to be together in spirit if not in reality. This is shown in some of the moving *lettres d'amour* which are available to the public eye. Thus, despite its artificiality and flamboyance, we read a suggestion of this phenomenon in a letter from Oscar Wilde to his wife: "... The messages of the gods to each other travel not by pen and ink, and indeed your bodily presence here would not make you more real: for I feel your fingers in my hair and your cheek brushing mine. The air is full of the music of your voice, my soul and body seem no longer mine, but mingled in some exquisite ecstasy with yours." (Hyde, 1948).

In theological literature we find the most explicit references to this phenomenon. Under the term "the sense of present reality" William James (1913) has described a feeling of objective presence, a perception of "something there", more deep and more general than any of the special and particular "senses" by which current psychology supposes existent realities to be originally revealed. James spoke of it as

a hallucination which is imperfectly developed. He quoted the experience of a close friend of his: "I have several times within the past few years felt the so-called "consciousness of a presence" . . . After I had got into bed and blown out the candle, I lay awake awhile thinking—when suddenly I *felt* something come into the room and stay close to my bed. It remained only a minute or two. I did not recognise it by any ordinary sense, and yet there was a horribly unpleasant "sensation" connected with it. It stirred something more at the roots of my being than any ordinary perception. . . . I was conscious of its departure as of its coming . . . The certainty that there in outer space there stood *something* was indescribably stronger than the ordinary certainty of companionship when we are in the close presence of ordinary living people. The something seemed close to me, and intensely more real than any ordinary perception."

This witness was described by James as being endowed with one of the keenest intellects he knew. In this person too, hypnagogic hallucinations of a tactile kind also occurred from time to time. The malefic and unpleasant associations of the visitant are noteworthy. But apparently on other occasions the idea of a presence may entail a quality of joyful elation.

"There was not a mere consciousness of something there, but fused in the central happiness of it, a startling awareness of some ineffable good. Not vague either, not like the emotional effect of some poem, or scene, or blossom, or music, but the sure knowledge of the close presence of a sort of mighty person." James went on to quote a writer in the *Journal of Psychical Research* (1895, p. 26) who proclaimed: ". . . suddenly, without a moment's warning my whole being seemed roused to the highest state of tension or aliveness, and I was aware, with an intenseness not easily imagined by those who had never experienced it, that another being or presence was not only in the room, but quite close to me."

This writer identified the visitant with a particular person—a friend of his. He was imagined as standing out of sight, behind and to the left. By slowly turning his eyes to the side, the writer could then see and recognise the gray-blue material of his trousers which appeared "semi-transparent, like tobacco-smoke in consistency". In other words, the idea of a presence had now given place to a visual hallucination.

Another instance was given by James. "Quite early in the night I was awakened . . . I then turned on my side to go to sleep again, and immediately felt a consciousness of a presence in the room, and singular to state, it was not the consciousness of a live person, but of a spiritual presence . . . I felt also at the same time a strong feeling of

superstitious dread, as if something strange and fearful were about to happen."

James also quoted the testimony of a friend of Flournoy who wrote: "Whenever I practice automatic writing, what makes me feel that it is not due to a subconscious self is the feeling I always have of a foreign presence, external to my body. It is sometimes so definitely characterized that I could point to its exact position. This impression of presence is impossible to describe. It varies in intensity and clearness according to the personality from whom the writing professes to come. If it is someone whom I love, I feel it immediately, before any writing has come."

Finally James described an example occurring in a very intelligent blind subject. He was liable to the fancy that a gray-bearded man clad in a pepper and salt suit, would squeeze himself under the crack of the door, and then cross the room towards a sofa. This would appear to have been merely an abstract conceit for the blind man possessed no vivid visual imagery, and no other special sense was involved in this idea of a presence.

In "Phantasms of the Living" that extraordinary sourcebook by Gurney, Myers and Podmore certain paragraphs are appropriate to our subject. The authors referred to what they call hallucinations of the lowest or most rudimentary grade. These consist in vague impressions of sense data without any actual stimulus being perceived. For example, they described cases where auditory hallucinations occur and yet no spectral words are actually heard, in the ordinary sense of the word. The voices seem to be formed and spoken within the chest; or the voices are regarded as being "soundless". Phenomena of this kind were equated by these authors with the "psychic hallucinations" described by Baillarger, in contra-distinction to ordinary psychosensorial hallucinations. In the visual sphere psychic hallucinations may reveal themselves as a type of delusion or potential hallucination which consists in the sense of a presence. An example was given where a normal person woke in the night with a curious feeling that his great friend, who was in India at the time, was in his room. He had an impulse to call out his name and although by now he was wide awake it took him some moments to realise that his friend could not possibly be there in the room. On yet another occasion the same person went to sleep having been thinking a good deal about his brother in America. In the middle of the night he woke up once again with the feeling that his brother was in the room and had been speaking to him. Yet another case was quoted where a subject had the feeling on many occasions that her sister was in the room. Sometimes the feeling

was so strong that she would get up and wander round the house looking for her sister.

Still upon the subject of religious mysticism and ecstasy, we may quote Janet, who observed the same phenomenon in his extraordinary patient Madeleine. Under the term *sentiment de présence* Janet described—none too lucidly—an intangible feeling of the all-pervading presence of the deity. Unfortunately, Janet did not discuss the phenomenon further and in simple language.

In works of a purely religious character, certain mystical experiences are often described, though it is usually difficult to distinguish between actual visions and less tangible mental and spiritual impressions of a presence. The phenomena detailed by Saint Teresa of Jesus (1515–1582) in her autobiography illustrate this difficulty. She was prey to diverse visions of which at least three types were identified, the bodily, the imaginary, and the intellectual. The last-named were the purest and loftiest of them all, and conform to our mundane ideas of an extracampine hallucination. "... I was in prayer one day ... when I saw Christ close by me, or, to speak more correctly, felt Him; for I saw nothing with the eyes of the body, nothing with the eyes of the soul. ... I went to my confessor in great distress, to tell him of it. He asked in what form I saw our Lord. I told him I saw no form. He then said: "How did you know that it was Christ?" I replied that I did not know how I knew it; but I could not help knowing that He was close beside me. ... For if I say that I see Him neither with the eyes of the body, nor with those of the soul ... how is it that I can understand and maintain that He stands beside me, and be more certain of it than if I saw Him? If it be supposed that it is as if a person were blind, or in the dark, and therefore unable to see another who is close to him, the comparison is not exact."

The writings of Brother Lawrence of the Resurrection (1591–1611) upon "The Practice of the Presence of God" are also relevant. "The presence of God is an applying of our spirit to Him, or a realization of His presence which can be brought about either by the imagination or the understanding.

I know of one who, for forty years, has practised the presence of God intellectually, and he gives it several other names ... he calls it ... an impression or a loving gaze or a sense of God. ... He says, however, that all these expressions for the presence of God are synonyms, they express the same thing, the presence which has come to be natural to him, in this way: By repeated acts and by frequently recalling his mind to God he has developed such a habit that, so soon as he is free from external occupations, and even while he is still busy,

his very soul, without any forethought on his part, is lifted above all earthly things. . . . It is this which he calls the actual presence of God which includes all other kinds and much more besides, so that he lives now as if there were only God and himself in the world: conversing always with Him, entreating Him at need and rejoicing with Him in a thousand ways."

Lhermitte, in his monograph *Mystiques et faux mystiques* (1952), has also briefly referred to this phenomenon as *le sentiment de présence*. He quotes two cases which may or may not be strictly relevant to our present series. The clinical history of his first patient makes dramatic reading. "Some years ago," wrote Lhermitte, "I received a visit from a man whose arrival was unusual, to say the least. To the maid who opened the door, he exclaimed: "Don't come near me. . . . He is there!" He was the devil." The patient who was a man of great learning submitted a long written narrative of his state of demoniacal possession. But on reading the text closely it seems probable that this patient was actually hallucinated, some of the time at least. Lhermitte's second patient concerned a lady who was secretary to a very important personage. For more than twenty years she had been attended by an imaginary handsome cavalier upon a magnificent horse. This phenomenon first appeared abruptly while she was walking down the *Avenue des Champs-Élysées*. The rider was always on her right-hand side. She could always see him but not clearly . . . the vision was more like a glistening shadow. It was almost but not quite constant; being more vivid when she was lonely, and absent if she was walking out of doors with someone else. It seems definite that this case was not so much an example of an idea of a presence, as an actual *hallucination d'un compagnon*. Lhermitte regarded the vision as a symbol of desires or trends which she did not dare declare.

Finally we may mention the idea of a presence as occurring in psychotics and more especially in schizophrenics. This topic formed the basis of the original paper by Jaspers (1913). Here the author described six cases of dementia praecox. The first patient said "I had the feeling that someone was inside me and then stepped out, perhaps out of the side or somehow. . . . I felt as if someone constantly walked by my side." The second patient would feel as if his father were in the room behind him. The third patient had the impression that someone was one or two yards behind her propelling her forwards though actually she felt no touch to her body. The fourth patient was more complex. When listening to music he was in the habit of making rhythmic movements. On occasions he would have the idea that his fiancée was standing behind him, back to back, making synchronous

and similar movements. His fifth patient wrote, "... I felt as though there were someone behind the bed who was writing down all my words." Jasper's sixth patient constantly felt as though someone were present, whom she could not see and who was watching her. The author quoted a patient of Forel's who had the notion that he was receiving messages though they were inaudible. The autobiography of Strindberg was also quoted. "... I sensed the presence of someone who had come there during my absence. I could not see him but I felt his presence."

DISCUSSION

The problem of the idea of a presence offers an interesting contribution to the study of sense-deception as a whole. It is strikingly evident from a scrutiny of the case-records and protocols, that the "idea" of a presence ordinarily constitutes a sort of rudimentary hallucination. There is every gradation between a feeling "as if" a presence were in the vicinity; through an intermediate stage of confident belief in the existence of an invisible, inaudible and intangible entity; up to finally an actual visual, auditory or tactile hallucination.

It is obvious that recourse to medical literature is poorly rewarding in a study of this phenomenon. Verbal discussion has, however, often raised other phenomena which are allied, to say the least, to this "idea" of a presence and which bear if not a relationship then at least a superficial resemblance. For example, when the idea of a presence entails the identification of the visitant as an *alter ego*, or one's other self, then we encroach immediately upon the territory of the *Doppelgänger*. Thus, closest in nature, is the "bipartition fantasy" or the phenomenon of the "emancipation of the ego" encountered in a variety of psychotic states. For example, an intelligent post-encephalitic psychopath began to develop at the age of 41 years the illusion of being two people. He could not actually see, hear or touch his other self, but he would imagine it occupying a definite position in space, to the side of but slightly behind the real body and out of sight. His *alter ego* would seem to urge him to do silly things. Urquhart's subject developed this same idea of doubling of the personality (the *alter ego* being imperceptible) under the influence of hashish. As he himself put it, "... the impression was that of wandering out of myself. I had two beings."

When the belief of duality becomes elaborated, and proceeds to a veritable hallucination, we attain the *heautoscopy* of Lhermitte (1951), or, as it used to be called "specular hallucinosis". Not infrequently the idea of a presence is equated with Capgras' syndrome. (Capgras and

Reboul-Lachaux (1923); Halberstadt (1923); Capgras, Lucchini and Schiff (1924); Capgras and Carrette (1924); Dupony and Montrassil (1924); Bouvier (1926); Vié (1928); Lévy-Valensi (1929); Dévine (1929); Larrivé and Jasienski (1931); Courbon and Tusques (1932); Coleman (1933); Dérombries (1935); Brochado (1936); Murray (1936)). But strictly speaking the term Capgras' syndrome should be confined to the mental phenomenon also called the "illusion of doubles" or—more usually—*l'illusion des sosies*. This refers to the non-recognition of familiar persons, with the postulation of imaginary differences and the further expressed belief that the real person has been replaced by a double. The factor of distinction is sometimes spoken of as the "negative double", the imaginary resemblances constituting the "positive double".

Using strictly these defining terms it is obvious that Capgras' syndrome bears no real relationship to the phenomenon which forms the topic of this paper. The same applies to the syndrome of Fregoli, or *le délire d'intermetamorphose* (Courbon and Fail (1919)); (Charpentier (1919)); Courbon and Tusques (1932)); (Daumezon (1937))¹. Though sometimes confused, this condition is quite different from the idea of a presence, being really a variant of Capgras' syndrome.

At times the idea of a presence can be looked upon as being almost the opposite phenomenon to the more common illusory states of unreality which may develop alongside the depersonalizations. It is not without interest that the same types of morbid condition—temporal epilepsy, confusional states, exhaustion, anoxia, narcolepsy, parietal lesions, ecstasy, hypnagogic twilight states—may be attended either by the symptoms of unreality (derealization) or by its opposite, namely the idea of a presence. This paradoxical experience, whereby a given symptom may stem from diametrically opposite pathologies, and moreover that diametrically contradictory clinical manifestations may develop with the very same type of lesion—is by no means rare in neurology, and deserves closer attention than it has received to date.

¹ The term *syndrome de Fregoli* needs explanation. Leopoldo Fregoli was an Italian actor, born in Rome in 1867, who excelled as a mimic. He was able to switch rapidly from one role to another with such success that he could produce single-handed a complete play, undertaking the roles of every character in the piece, male or female.

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SURVEY OF 1000 CASES OF APOPLEXIA CEREBRI

By

T. DALSGAARD-NIELSEN

In the present paper a survey will be taken of 1000 cases of apoplexia cerebri which during the years 1940-53 were admitted to the Neurological Department of Frederiksberg Hospital, in order to throw light on the problems arising in connexion with the investigation and treatment of neurogeriatric disorders.

All things considered, the higher age-classes of the population have no appreciably greater frequency of illness than the lower age-classes, as i.a. has been shown by V. Kampmann (1) in a statement of the material of insured persons of the insurance company Hånd i Hånd. The statement, however, shows that 50 per cent. of all diseases have a greater duration of illness in older than in younger people, and that in the older people diseases of long duration are of particularly frequent occurrence. These special categories of diseases, the geriatric disorders, will always have a claim to great interest because of the great duration of the disease, the high degree of disablement often involved, and the high mortality. This is further stressed by the fact that they will numerically come to characterize medical statistics increasingly because of the displacement in the distribution according to age within the population towards an increase in the case of the higher age groups which has taken place in recent years. Thus the following figures may be adduced from Denmark:

The number of persons above 65 years of age constituted 6.8 per cent. of the population in 1921, 7.8 per cent. in 1940, and 9.7 per cent. in 1950. While the increase during the period 1940-1950 among persons below 20 years was 13.8 per cent. and in the age group 20-64 years 7.8 per cent., it was 29.7 per cent. among persons above 65 years.

In previous works by Axel Pedersen and T. Dalsgaard-Nielsen (2, 3) we counted the elderly patients in the Neurological Department of Frederiksberg Hospital for the years 1948 and 1949 and found that no

less than 26 per cent. of all the 2408 patients treated were more than 60 years of age. Furthermore, we found that the time of stay in hospital for patients with geriatric complaints was longer than the average time spent in the reception department (1949: 31 days), but otherwise the difference was not so great as we had expected, due to the numerical displacement involved in the high mortality rate of these cases during the first days. We obtained a better impression of the time of stay in hospital for geriatric patients by investigating conditions of the patients with such diseases whom, after completed examination and treatment, we might transfer to the Department for Chronic Diseases. There the average time of stay proved to be 141 days.

Among the geriatric disorders the neurogeriatric ones will not be the least dominant ones. I am thinking of the senile, arteriosclerotic, or hypertensive encephalopathies, more especially apoplexia cerebri. Undoubtedly these complaints are the main cause of disorders in the central nervous system, in Denmark being the third most frequent cause of death, next to cancer as number two and cardiac diseases as number one.

Because of what has been said above and especially because cases of apoplexia cerebri in the municipality of Frederiksberg are admitted to and treated in the Neurological Department, we have taken a special interest in this very disorder, and our interest has been further accentuated by the fact that we have learnt that it is not without value to utilize to the utmost degree the possibilities of treatment available because the mortality rate may be reduced and the degree of disablement, too.

During the preparation of the material of the department the work has been divided into a number of special tasks, about which a number of communications have previously been published (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16), but in order to facilitate the survey and preserve the continuity a full presentation will be given in broad outline in the present paper.

The rough starting material is based on an examination of the case records of patients discharged from the Neurological Department under the diagnosis of apoplexia cerebri, beginning by April 1st, 1940, when the department was established, and concluding by October 1953. The year-classes of 1940 and 1953 thus are not complete.

The patients come from a special metropolitan area, the municipality of Frederiksberg, the population of which by November 7th, 1950, amounted to 118,993 and is fairly stationary because the building up of the area of the municipality is far advanced. The municipality of Frederiksberg enters geographically as a central part of the metro-

politan area of Greater Copenhagen, the population of which by November 7th, 1950, amounted to 974,901 or, including the surrounding municipalities, 1,168,340.

At the examination of the material of the case records it proved necessary to discard some patients, partly because the case sheets were defective, partly because the diagnoses were judged to be clinically untenable. For reasons of numerical technique it had in advance been found desirable to stop at a number of patients of 1000, for which reasons the last patients admitted in 1953 have not been included, the year-class of 1953 thus, as mentioned above, being slightly incomplete. However, the number of patients not included in the material only amounts to 42.

1000 cases of apoplexia cerebri thus are left. The very number is such that we found it probable that working up of the material might give valuable information. Furthermore, the material must be said to be marked by a certain uniformity, partly because the recording of the cases and the examinations have been made on the same lines through the years, partly because the same criteria have been made the basis of diagnostics and differential diagnostics, and finally because the therapeutic milieu and the treatment itself have been the same during the years.

The material can no doubt be taken as a significant expression of hospitalized cases of apoplexia cerebri in a metropolitan population of the structure of the municipality of Frederiksberg. No cases of apoplexy from other municipalities have been admitted to the department, and admission of Frederiksberg cases of apoplexy to other departments has taken place to a very slight extent only. It may be mentioned, e.g., that I have examined the number of admissions of cases of apoplexy to the departments of Medicine of Frederiksberg Hospital and to the other hospital situated in the municipality of Frederiksberg, Diakonissestiftelsen, and found that it was a question of 30-40 cases a year in all, and that an appreciable number of these cases, for that matter, came from the municipality of Copenhagen. On the other hand, we have no information about the number of cases of apoplexia cerebri treated in the homes. Presumably these have either been very light cases or severe cases in which death supervened very soon; but it is impossible to guess at the exact number. It should be mentioned that *Krabbe* (17) has called attention to the fact that the municipality of Frederiksberg as regards composition according to occupation and age is hardly significant of Greater Copenhagen, and therefore an application was made to the Statistical Department, which readily put a statement for the years 1940 and 1950 at my disposal from which it appears

that the population in Frederiksberg on an average is somewhat older than that of Copenhagen as the part of the population found in the age-classes above 45 years is greatest in all groups in Frederiksberg, and that the difference is greatest in the highest ages. Furthermore the statement reveals a difference in the composition of the population according to occupational employment, as there are comparatively much fewer workers and more independent business people and employees than in Copenhagen, just as, in accordance with the age structure, there is a comparatively higher number of retired officials and old-age pensioners in Frederiksberg.

By the comb-out of the material which we have made, we have utilized the punched-card principle, system Erwol, and so far we have asked well over 200 questions of the material. The questions include partly the quite common ones such as sex, age, the age when the apoplexy started, group division into thrombosis, hemorrhage, and emboli, etc., partly conditions of more special interest, such as aphasia, symptoms of the pyramidal tract, conditions of the pupils, disablement, mortality, etc., as appears from the following list of all questions:

Name

0-3	Year of case history	39	Hospitalized within the first 24 hours
4-7	Age group		
8	Male	40-41	Previous attacks
9-10	Heredity of apoplexy	42-43	Acute
11-12	Occupation	44-45	Loss of consciousness
13	Not active	46-47	Weight
14-15	Health		
16	Reserve		<i>First 24 hours in hospital</i>
17-18	Type of apoplexy	48	Cyanosis
19	Arteriosclerosis	49	Pale
20	Hypertensio arterialis	50	Cold
21	Heart disease	51	Warm
22	Chronic nephropathy	52	Perspiring
23	Diabetes	53	Cheyne-Stokes respiration
24	Lues	54	Other abnormal types of respiration
25	Other diseases	55	Pathological function of heart
26	Abuse of alcohol	56	Edema
27	- , not stated	57	Worn out
Provoking cause		58	Psychical disturbance
28	Psychical	59	Pathological visual field
29	Somatic	60	Paralysis of conjugate gaze
30	During sleep	61	Paresis of ocular muscles ¹
31	No provoking cause	62	Pupillary changes
32	Not stated	63	Disturb. of the trigeminus nerve
33-36	Month		
37-38	Actual prodromes		

64	Disturb. of the facial nerve	122-123	Pathological sedimentation rate
65	Disturb. of the acoustic nerve	124	Systolic blood pressure above 150
66	Bulbar character ²	125	Diastolic blood pressure above 100
67	Paresis of the accessory nerve	126-127	Pathological electrolyte findings
68	Paresis of the tongue	128-129	Temperature
69	Aphasia	130-131	Course during first 24 hours
70	Motor paralysis of the upper extremity		<i>During stay in hospital (incl. first 24 hours)</i>
71	Motor paresis of the upper extremity	132	Cyanosis
72	Sensory paresis of the upper extremity	133	Pale
73-74	Tonus findings	134	Cold
75-76	Reflex findings	135	Warm
77	Motor paralysis of the lower extremity	136	Perspiring
78	Motor paresis of the lower extremity	137	Cheyne-Stokes respiration
79	Sensory paresis of the lower extremity	138	Other abnormal types of respiration
80-81	Tonus findings	139	Pathological cardiac function
82-83	Reflex findings	140	Edema
84-85	Unilateral Babinski	141	Worn out
86-87	Unilateral Oppenheim	142	Psychical disturbances
88-89	Unilateral Rossolimo	143	Pathological visual field
90-91	Unilateral abnormal abdominal reflexes	144	Paralysis of conjugate gaze
92-93	Bilateral Babinski	145	Paresis of ocular muscles ¹
94-95	Bilateral Oppenheim	146	Pupillary changes
96-97	Bilateral Rossolimo	147-148	Arteriosclerotic retinopathy
98-99	Bilateral abnormal abdominal reflexes	149-150	Hypertensive retinopathy
100	Doubtful reflex findings	151-152	Other pathological ophthalmological findings
101-102	Disturbances of the sphincter function	153-154	Pathological findings in ear clinic
103-104	Right-sided hemiparesis	155	Disturbance of the trigeminal nerve
105-106	Crossed hemiplegia	156	Disturbance of the facial nerve
107-108	Right-handed	157	Disturbance of the acoustic nerve
	<i>First examinations</i>	158	Bulbar character ²
109	Lumbar puncture performed	159	Paresis of the accessory nerve
110	Normal cerebrospinal fluid	160	Paresis of the tongue
111	Pathological cerebrospinal fluid	161	Aphasia
112	Blood in cerebrospinal fluid	162	Motor paralysis of the upper extremity
113	Artificially blood in cerebrospinal fluid	163	Motor paresis of the upper extremity
114-115	Blood urea above 50	164	Sensory paresis of the upper extremity
116-117	Blood sugar above 110	165	Bilateral paresis of the upper extremity
118-119	Pathological urine		
120-121	Pathological hemoglobin percentage		

166 Motor paralysis of the lower extremity		<i>Later examinations</i>
167 Motor paresis of the lower extremity		127 Lumbar puncture performed
168 Sensory paresis of the lower extremity		128 Normal cerebrospinal fluid
169 Bilateral paresis of the lower extremity		129 Pathological cerebrospinal fluid
		130 Blood in cerebrospinal fluid ³
		131 Artificially blood in cerebrospinal fluid
<i>Tabulated on the back of the card</i>		132 133 Blood urea above 50
100 Reserve		134 135 Blood sugar above 110
101 Reserve		136-137 Pathological urine
102 Reserve		138-139 Pathological hemoglobin percentage
103-104 Unilateral Babinski		140-141 Pathological sedimentation rate
105 106 Unilateral Oppenheim		142 143 Systolic blood pressure above 150
107 108 Unilateral Rossolimo		144-145 Diastolic blood pressure above 100
109-110 Unilateral abnormal abdominal reflexes		146 147 Pathological electrolyte findings
111-112 Bilateral Babinski		148 149 Temperature
113-114 Bilateral Oppenheim		150 151 Course after first 24 hours
115-116 Bilateral Rossolimo		152 154 Working capacity on discharge
117-118 Bilateral abnormal abdominal reflexes		155 157 Duration of stay in hospital during each attack
119 Doubtful reflex findings		158 Section
120 121 Disturbances of sphincter function		159 (Eugenics)
122-123 Crossed hemiplegia		
124 125 Changes of tonus and reflexes		
126 Reserve		

The clinical diagnosis in the material is based on the following definition:

Under the clinical diagnosis of apoplexia cerebri are included cases of very acute, acute, or subacute incipient signs of pathological brain function, lasting for a certain time (at least 24 hours), and with a clinical basis of the view that they have been directly produced by a vascular catastrophe (hemorrhage, thrombosis, emboli) in a cerebral vessel on the basis of a not proper local intracranial complaint, e.g. arteriosclerosis, hypertension, senium, nephropathy, heart disease, diabetes mellitus, uratic diathesis, polycythemia, adiposity, lues, etc.

A special group consists of cases of thrombosis in the extracranial course of the carotid artery which may be demonstrated by palpation or auscultation.

As a complication there may be a penetration to the ventricular system or the subarachnoid space.

According to this definition cases with clinical symptoms of the following vascular states are outside the group of apoplexia:

Chronically developed states (encephalopathies, atrophies), primary intraventricular and subarachnoid hemorrhages, traumatic hemorrhages, infections (sinus thrombosis, cortical phlebitis), aneurysms (hemorrhage, thrombosis), tumor hemorrhage, transitory cerebral anoxia and edema on a vascular basis, and vascular catastrophes in the cerebellum, pons, and medulla oblongata.

Among the cases admitted to the department under the diagnosis of apoplexia cerebri, there have been numerous ones in which this diagnosis in our estimation could not be maintained. To throw light on the question what pathological states have been of actual importance to the differential diagnosis in relation to other disorders, a survey will be made of the complaints which in our material have been concealed under the admission diagnosis of apoplexia cerebri.

1. Transitory cerebral anoxiae and edemas in hypertensive or arteriosclerotic cerebral disorder. 2. Rupture of extracerebral vessels with or without any demonstrable aneurysm. 3. Acute traumatic changes in the brain. 4. Gliomas with hemorrhage or edema. 5. Intracerebral metastases. 6. Acute syncopes with cerebral anoxia because of heart disease. 7. Acute febrile states, e.g. pneumonia with confusion. 8. Acute intoxications, e.g. overdose of sleeping drugs. 9. Uremia. 10. Diabetic coma. 11. Hypoglycemia (insulinism, insuloma). 12. Hysteria. 13. Paralytic fits. 14. Attacks of migraine of an ophthalmoplegic, paresthetic, or cerebellar type. 15. Cerebral Quincke's edema. 16. Coma after epileptic fit. 17. Carotid sinus syndrome. 18. Heat-stroke, sunstroke. 19. Fracture of the collum femoris.

Separately these pathological pictures may present points of resemblance with apoplexia cerebri, but while some of them are fairly easily separated from this disorder, there are others in which more comprehensive examinations are required, and a few may in spite of minute examination remain uncertain from the point of view of differential diagnosis

An especially significant problem occurs in the differential diagnosis within the group of apoplexy between hemorrhage, thrombosis, and emboli, not least because the correct differential diagnosis may here

be decisive of the choice of certain modern possibilities of treatment, such as surgical intervention and anticoagulation treatment. In our material we have observed the following rough clinical basic rules:

Apoplexia embolica cerebri:

The symptoms set in very acutely.

The patients are often youngish persons with good vessels, without hypertension, but with heart disease. The extent of the process is slight. There is a fast decrease of the symptoms.

Apoplexia haemorrhagica cerebri:

The symptoms set in very acutely or acutely. The patients are both elderly and youngish persons with hypertension or arteriosclerosis. The symptoms may subside fairly quickly. They are often provoked by acute exertion. In certain cases there is blood in the cerebrospinal fluid. Cerebrospinal fluid without blood does not exclude the diagnosis.

Apoplexia thrombotica cerebri:

The symptoms set in acutely or subacutely. May appear both in elderly and youngish persons with arteriosclerosis or heart disease. The symptoms will often progress during the first time after onset of the stroke. May develop during sleep. No blood in cerebrospinal fluid.

It is a well-known fact that these rough lines hitherto followed have proved insufficient, and so the results of our working up of the material must be judged with the reserve thus involved.

At the numerical statement of our material and at the statistical calculations and estimates on which the survey is based, the Board of Health have put their expert knowledge at our disposal, for which I am much obliged to the Board.

SURVEY OF THE MATERIAL

1. Occupation.

It has been of interest to ascertain the occupation of the patients. It appears from Table I that the men were mainly manual workers, only to a less degree brain workers, and that the women mainly described themselves as housewives, which undoubtedly does not exclude that many of the women had some occupation out of their homes

and only is expressive of the fact that the women in question themselves considered their activities as housewives as their main occupation. The result hardly shows anything but what might be expected when no especially detailed inquiries occur on the case sheets. Such inquiries will undoubtedly be necessary if we are to attain to any estimate of the problem what causal relation may exist between occupation and apoplexia cerebri.

TABLE I
Percentage distribution according to occupational groups.

	Men	Women	In all
Brain workers	27.0	6.2	14.7
Manual workers	53.4	6.1	25.4
Housewives	—	79.7	47.2
Others	19.6	8.0	12.7
	100.0	100.0	100.0

2. *Premorbid Status.*

We have been interested in the question whether the fits of apoplexy befell patients who previously considered themselves ill or healthy, consideration being had to age. In advance it was to be expected that the health of most patients was so materially influenced by the fundamental disease on the basis of which the apoplectic catastrophe supervened that they would themselves have felt induced to emphasize it; but it appears from Table II that almost three fourths of the patients stated that they were in good health prior to the catastrophe, and that only one fourth had an impression that their health was poor. A greater part of the men than of the women were in good health; a difference which is significant. It may be concluded that apoplexia cerebri in the case of three fourths of the patients set in in apparently healthy persons.

TABLE II
Percentage distribution according to health.

	Men	Woman	In all
Good	78.4	68.9	72.8
Poor	18.9	29.2	25.0
Not stated	2.7	1.9	2.2
	100.0	100.0	100.0

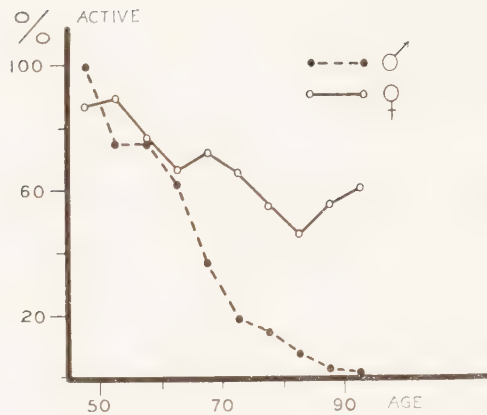


Fig. 1.

3. Occupational Activities.

In connexion with the patients' health we have tried to get information about their social capacity and to learn whether they were still active or not in their occupation. As seen in fig. 1 the percentage number of active persons in each age group has been registered for either sex, from which it appears that between 75 and 100 per cent. of both men and women were active up to the age of 60–65 years. In the higher age groups there is a dissociation, the women mainly remaining active while the activity decreases greatly in the case of the men. I explain this dissociation by the numerous housewives who dominate the material remaining active housewives into the high age, whereas the men at the very age mentioned are pensioned off, obtain old age pension, and retire from their jobs. The difference thus is more expressive of the difference of occupation than of a difference in working capacity. It may be concluded that while the great majority of cases of apoplexy in men occur in persons who are no longer active in any occupation and thus are not put to any direct decrease in income because of the possible chronic disablement, the great majority of women suffering from apoplexy will because of their occupational insufficiency lose the basis of a maintenance of their previous standard of living.

4. Distribution According to Sex.

In the material there are 40 per cent. men (408) and 60 per cent. women (592). In fig. 2 the number of men is indicated in percentages of the total material registered for the calendar years 1940–1953, and

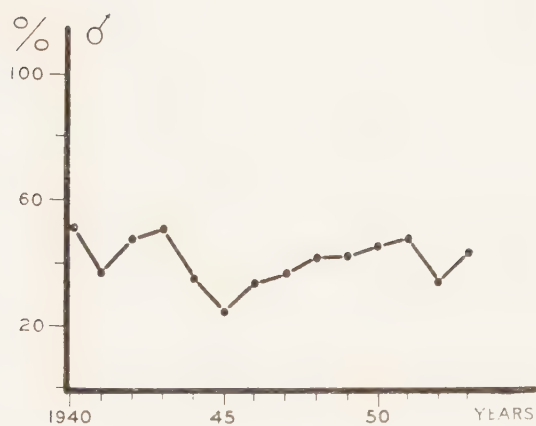


Fig. 2.

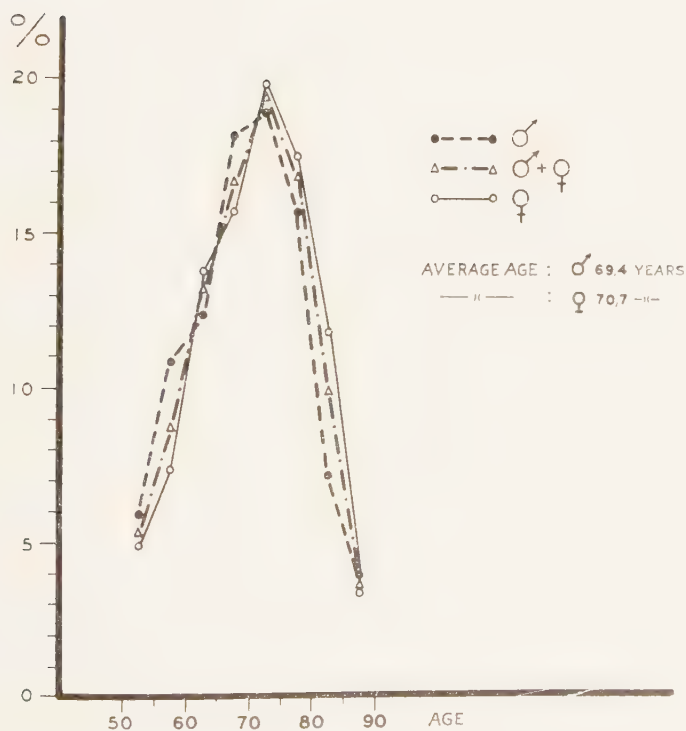


Fig. 3.

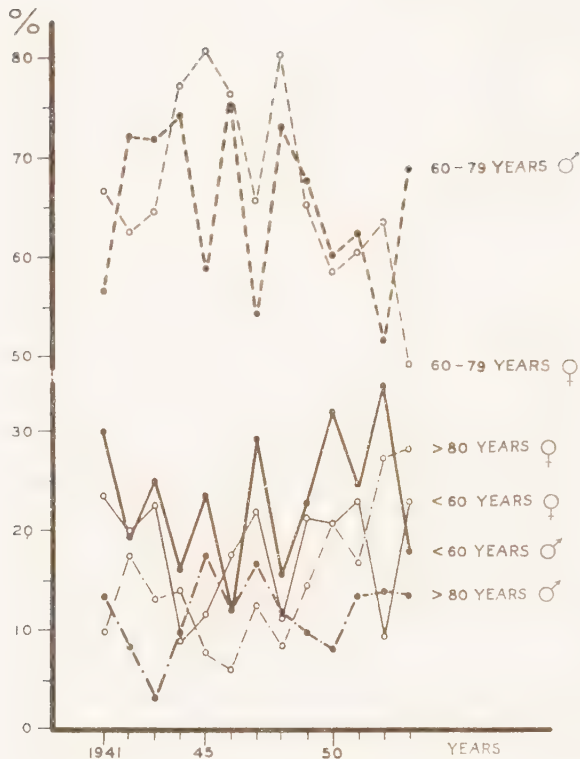


Fig. 4.

it is seen that there is no systematic difference in the distribution according to sex through the years. One of the reasons for the excess of women among hospitalized patients may undoubtedly be the fact that the wife will often be able and ready to nurse her sick spouse in the home, while the husband will mostly be unable to do so. It should be kept in mind that the distribution according to sex only refers to hospitalized apoplexies.

5. Age at the Onset of the Apoplexy.

It has been of importance to have cleared up at what age the apoplexy sets in fig. 3, in which the percentage distribution appears from three curves for respectively men, women, and men + women, shows that the three curves accompany each other, and that the great majority of the apoplexies occur in the ages of 60-79 years. The average age for men and women is about 70 years, and there is no significant difference between the average ages for men and women. In fig. 4 we have

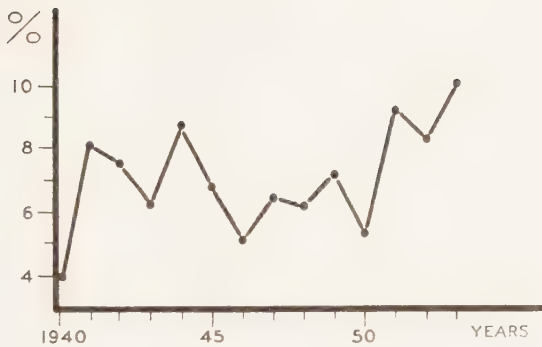


Fig. 5.

illustrated the percentage distribution of the age of onset in the various calendar years, and it will be seen that there is no tendency towards a different distribution according to age in the various calendar years.

6. The Frequency of Apoplexy.

The number of emboli in the material was 68 (7 per cent.), viz. 20 men and 48 women; the number of hemorrhages was 432 (43 per cent.), viz. 177 men and 255 women, and the number of thromboses was 500 (50 per cent.), viz. 211 men and 289 women. It is seen that the excess of women in the material asserts itself in all the three groups.

Hemorrhage occurred with the same frequency in men (43.3 per cent.) as in women (43.2); the same applies to thrombosis with 51.7 per cent. in men and 48.8 per cent. in women, whereas emboli occurred

TABLE III

Age	Census 15 6 1945		Apoplexies per thousand	
	M	W	M	W
< 50	36111	43523	0.8	0.7
50-54	3470	4548	6.9	6.4
55-59	2936	4131	15.0	10.4
60-64	2457	3744	20.4	21.6
65-69	2035	3122	36.4	29.8
70-74	1354	2231	56.9	52.4
75-79	834	1448	76.7	71.8
80-84	340	776	85.3	90.2
85-89	122	325	131.1	61.5
90	17	60	58.8	83.3
	49676	63908	8.2	9.3

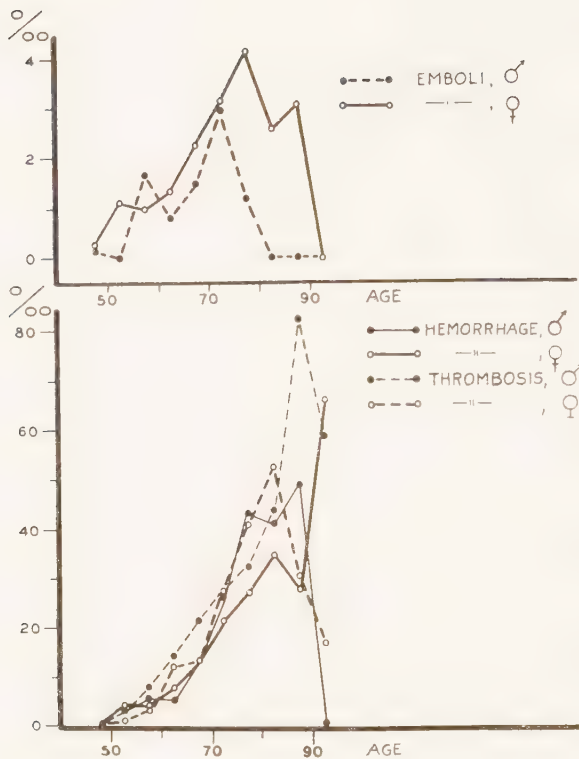


Fig. 6.

in women with a frequency of 8.1 per cent. and in men with a frequency of 4.9, a difference which, however, because of the small number of emboli does not allow of any conclusion.

We have tried to put the number of apoplexies in relation to the population figure, as appears from Table 3. The frequency of hospitalized cases of apoplexy is seen to be 8.2 per thousand for the men and 9.3 per thousand for the women for the whole series of years covered by the material, i.e. that during a 13½ year period 8-9 per thousand of the population are hospitalized because of apoplexia cerebri.

If we look at the various age groups in the table, it appears that the frequency of apoplexy increases with age and almost constantly is lower for women than for men at the corresponding age. Furthermore, we have investigated the problem whether within the period 1910-53 there was any change in the occurrence of apoplexy. Fig. 5, which is a registration of the cases of apoplexy indicated in percentages of the material in the various calendar years, shows some variations, but

TABLE IV
Percentage mortality.

	Men	Women	In all
Hemorrhages	60.5	63.1	62.0
Thromboses	32.2	28.7	30.2
Emboli	35.0	35.4	35.2
In all	44.6	44.1	44.3

hardly any systematic development. In this connexion it should be kept in mind that this is a question of the frequency of hospitalized cases, and besides, we cannot without further circumstances disregard the fact that in the course of time there may be a change in the principles on which admission to hospital of these patients is based. In conclusion it may be said that the frequency of cases of apoplexy hospitalized during a 13½ year period is 8-9 per thousand, that the frequency of apoplexy increases with age, and that it is higher among women than among men.

It has been investigated whether the frequency of emboli, thromboses, and hemorrhages changes with the age of the patients, and, as appears from fig. 6, which indicates the frequency in the various age groups of men and women for both emboli, thrombosis, and hemorrhage, indicated in number per thousand of the whole material, it is remarkable that the frequency of thrombosis is essentially higher than the frequency of hemorrhage in elderly patients, especially in the case of men. In the case of the emboli the figures are too small for any safe conclusions to be drawn.

7. Mortality.

In Table 4 the percentage mortality is indicated. It is seen that the mortality rate is 44.3 per cent., viz. 44.6 among men and 44.1 per cent.

TABLE V
Working capacity on discharge.

	Men	Women	In all
Dead	44.6	44.1	44.3
Helpless (0)	10.3	10.3	10.3
Heavily disabled (0-1/3)	25.5	26.7	26.2
Moderately disabled (1/3-2/3)	11.3	14.2	13.0
Slightly disabled (2/3-1)	8.3	4.4	6.0
No disablement (1)	—	0.3	0.2
	100.0	100.0	100.0

among women, a difference which is not significant. In the case of the subgroups of hemorrhage, thrombosis, and embolus there is no significant difference in mortality among men and women, either. On the other hand the hemorrhage mortality is significantly higher (62 per cent.) than the thrombosis mortality (30.2 per cent.) and the embolus mortality (35.2 per cent.). The difference between thrombosis mortality and embolus mortality is not significant.

8. *Postmorbidity Status.*

At the discharge of the patients from the department a statement of the estimated disablement as a whole with deference to the age of the person in question is consistently entered on the case sheets. It appears from Table 5, in which the patients are divided into six different groups of disablement and in which the figures are percentages of the total material, that a very considerable number of the patients are helpless or heavily disabled and that only a slight number are moderately or slightly disabled, and that practically no patients are without disablement. The only significant difference in the working capacity of men and women on discharge is that among the men a higher number are only slightly disabled.

Converting the figures of invalidity into percentages of those surviving, we get the following figures:

Helpless 19 per cent.

Heavily disabled 47 per cent.

Moderately disabled 23 per cent.

Slightly disabled 11 per cent., and

Not disabled less than 1 per cent.

It appears from the figures that the methods of treatment hitherto used involve a very high mortality and among the surviving patients a considerable disablement; but there is reason to believe that by a changed and more intensive treatment it is possible to reduce mortality, and that by an energetic rehabilitation it will be possible to transfer a considerable number of the patients from the groups of helpless and heavily disabled to the other groups.

SUMMARY

After a preliminary documentation of the displacement of the distribution of the population according to age towards an increase within the higher age groups and hence of an increasing need for measures in the case of geriatric and especially neurogeriatric diseases,

the author discusses a material of 1000 cases of apoplexia cerebri which have been admitted to the Neurological Department of Frederiksberg Hospital during the period 1940–1953.

It has been tried to throw light on the apoplectic disorder by means of a punched-card system with well over 200 questions.

The clinical criteria for the diagnoses of hemorrhage, thrombosis, and emboli are indicated, and a number of complaints which from the point of view of differential diagnostics have been of actual interest in the material, are mentioned.

The material is discussed with reference to occupation, premorbid status, premorbid occupational activity, distribution according to sex, age at onset of apoplexy, frequency of apoplexy, mortality, and post-morbid status.

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VESTIBULO-OCULAR REFLEX DISORDERS IN A CASE OF TRANSTENTORIAL HERNIATION AND FORAMINAL IMPACTION OF THE BRAIN STEM

By

SVEN ETHELBERG

Although severe secondary affection of the brain stem by way of transtentorial herniation is a common occurrence in the late stages of supratentorial space-taking lesions, reports on disordered ocular movements in the nature of gaze paralyses seem to be extremely rare in such cases. There are a few observations on record, of space-taking subtentorial lesion, leading to secondary affection of the brain stem with gaze paralyses. *Bucy and Weaver* (1) have reported three cases of cerebellar abscess in which ipsilateral paralysis of lateral conjugate eye movements was found. These disorders disappeared after removal of the cerebellar abscess. *Madonick* (2) has reported a case of cerebellar tuberculoma in which gaze disorders in the nature of anterior internuclear ophthalmoplegia were disclosed. Pathoanatomical examination revealed no immediate affection of the brain stem. The last-named writer reviewed a brief series of ocular disorders occurring in subtentorial tumours.

It should be noted, however, that the patients in the cases referred to were co-operative to the extent that voluntary movements and follow movements could be examined. When in supratentorial space-taking lesions the reports are rarer, this is probably bound up with the fact that in patients having severe secondary affection of the brain stem by notching of the mesencephalon and by foraminal impaction of the medulla, concomitant disorders of consciousness are present in the nature of severe disturbances of wakefulness (sopor and coma). These patients are unco-operative so that voluntary eye movements and follow movements cannot be tested.

Recently *Klingon* (3) succeeded in demonstrating, in a comatose patient with a primary lesion of the brain stem, disorders of the con-

jugate movements of the eyes after cold caloric stimulation of the ear. This mode of disclosing vestibulo-ocular disorders was utilized by *Ethelberg* and *Værnel* (4) in demonstrating disorders of conjugate eye movements similar to those seen in anterior internuclear paralysis. This was done in three cases of supratentorial space-taking lesions in which a sudden and severe herniation of the brain had developed.

But "ophthalmoplegia internuclearis anterior" is only one type of disordered vestibulo-ocular reflex. In the following, a case displaying more complex and obscure disorders after cold caloric stimulation will be reported.

CASE RECORD

A.K.H. G.: 11989. Admitted on October 31, 1952. A man of 50 who for 3 months before admission had displayed increasing loss of initiative and loss of memory; his actions had become peculiar; the feeling tone had become shallow, and eventually somnolence and apathy and mild disorders of gait supervened. Lumbar puncture made in his regional hospital revealed a spinal pressure of 290 mm of water, normal cell count and protein content.

On examination he displayed shallow facetious reactions, interspersed with brief periods of shallow depressive states. He was disoriented as to time and place. There was a marked loss of memory for remote and recent events. A moderate loss of power was disclosed in the left arm and leg together with a severe left lower facial weakness. No definite abnormalities in muscular tone or in deep and cutaneous reflexes could be revealed. Roentgenograms of the lungs showed enlargement of the left hilus and an irregular shadow in the left lower lobe. Roentgenograms of the skull were normal. Laboratory tests showed mild simple anaemia. Sedimentation rate 70 mm. Wassermann reaction in blood negative.

His state of wakefulness was varying from deep somnolence from which it was difficult to arouse him, to mild somnolence from which he could be made co-operative to some degree on powerful commands. During the ophthalmological examination which was performed on November 1, co-operation was poor. The visual activity and the visual field could not be examined. There was a mild tendency for the left eye to turn downward, and also a tendency to divergent strabismus. There was difficulty in lateral conjugate movements, although they could be performed for brief periods. Upward gaze movements could not be obtained while downward gaze was intact. The right pupil was larger than the left with no reaction to light. Bilateral choking of the optic discs.

On November 4, a routine otological examination was made revealing no abnormalities in hearing; audiometry could not be completed because of lack of co-operation. A caloric vestibular test, in which water of 27 centigrades was employed, showed normal conditions. Later, on the same day, a cold caloric vestibular test was made in which ice water was used. At the beginning of the test he was markedly soporous, reacting only to painful stimuli and with an inappropriate 'yes'. The upper lids were limply semi-closed. Blood pressure had gradually risen to 190 systolic, the pulse rate varied from 52 to 64. One hour before the test the right pupil was a little larger than the left; on testing the right pupil was a little smaller than the left, with prompt reaction to light on the two sides. The right eye was abducted a few degrees. There was no co-operation as to voluntary eye movements or follow movements. As judged by spontaneous movements of the eyes no indication of severe ocular or gaze paralysis could be disclosed, though spontaneously performed gaze movements upward were not seen.

The test was made by irrigating the external auditory canal with 20 ml of ice water (3–5° C.). The intervals between the conclusion of one test and the beginning of another was at least 2 minutes.

(A.1) Right ear: After a latency period of 75 seconds after completion of the irrigation a mild and rapidly transient bilateral adduction of the eyes developed. No further reaction was noted. No nystagmus.

(A.2) Right ear (repeated): After 30 seconds questionable beginning tonic conjugate deviation to the right; after 45 seconds this was definitely so. The adduction of the left eye was more marked than was the abduction of the right. Slow nystagmus movements towards the left appeared after 45 seconds, lasting for another 45 seconds. For 30 seconds tonic lateral fixation as described above with no nystagmus until after 120 seconds of eye movements the initial position was slowly assumed.

(A.3) Left ear: No response (120 seconds).

(A.4) Left ear (repeated): After a latency period of 25 seconds and lasting for 180 seconds a slow tonic deviation of the eyes to the left developed, at the same time slow nystagmus movements towards the right were observed in both eyes. The adduction of the right eye was more marked than was the abduction of the left. There was an additional downward movement of the adducted right eye.

At this stage 200 ml. 50 per cent. glucose was administered intravenously. During the injection the patient woke up. It was possible to follow from second to second his increasing orientation. His answers

were immediate and prompt and generally appropriate. No change in the powerlessness of the limbs came on. Although eventually becoming fully awake, he would not realize anything being wrong with his left arm (dyssomatognosis). After the administration of glucose the pupils were equally large with normal reaction to light and convergence movements. There was no strabismus, and the monocular and gaze range of movement were normal.

A cold caloric test was then repeated in either ear.

(B.1) Right ear: After a latency period of 30 seconds a slow sub-maximum tonic deviation occurred *to the left*. As in the previous tests, the adduction was more marked than the abduction. Conspicuously slow nystagmus movements to the right were transiently noted. The deviation of the left eye was only a few degrees beyond the midline laterally; while the right eye was maximally adducted and intermittently turned (and rolled?) downwards. After 180 seconds brief adduction movements in the left eye were observed with irregular intervals; while the right eye remained in maximum adduction and mild downward displacement. After 240 seconds the original position was obtained on either side.

(B.2) Left ear: After a latency period of 20 seconds tonic deviation of the eyes to the left developed unassociated with nystagmus. The adduction was more marked than the abduction. After 50 seconds the deviation became intermittent, the "backward" movements not being of the nystagmus type. After 60 seconds slow nystagmus movements to the right were observed simultaneously in both eyes. The starting position with no movements was obtained after 150 seconds.

During the following days his condition was unchanged. Angiograms were made after injection into the right common carotid, showing an angiographic configuration in the frontal region as is seen in cases of metastatic cerebral tumours (*Ethelberg and Værnet*, 5). There was a marked downward displacement of the central venous system, indicating a severe herniation of parts of the brain through the tentorial incisure.

Tapping of the right occipital horn was unsuccessful. A rise in pressure to 330 mm of water was measured, but fluid was not emitted with certainty.

A diagnosis of pulmonary carcinoma with intracerebral metastasis was made. Consequently operation was deemed futile, and the patient was transferred to his county hospital. He died one month later.

At autopsy a pulmonary carcinoma was disclosed. Autopsy of the brain revealed a metastatic tumour from a pulmonary carcinoma, extending from the anterior part of the right anterior horn through a

deep part of the hemisphere, just lateral to the ventricle, backward to the region of the trigonum. The brain was not fixed *in situ*; consequently, the degree of transtentorial herniation could not be ascertained at autopsy, but a mild cerebellar pressure cone was visible. A thorough examination of the brain stem and the cerebellum did not reveal any sign of metastatic tumour, or hæmorrhagic lesion.

COMMENT

For the purpose of the following discussion the main features of the case reported are, first of all, the occurrence of marked disorders of the vestibulo-ocular reflex. This was so despite the fact that the space-taking lesion was purely supratentorial. Since this type of reflex disorder is indicative of a lesion within the brain stem, in so far, at least, as labyrinthine lesions can be precluded, and since no primary affection of the brain stem was disclosed at autopsy, it would seem reasonable to take the vestibulo-ocular changes as something ensuing upon a secondary affection of the brain stem, caused by the supratentorial space-occupying lesion; that is, upon a transtentorial herniation of the midbrain and a foraminal impaction of the medulla. There is a number of clinical changes that would seem to corroborate this assumption.

As far as the gross pathoanatomical changes of the brain are concerned, the autopsy report cannot be taken as conclusive in this respect. No fixation of the brain was made *in situ*; and even if signs were found of foraminal impaction of the medulla and the cerebellar tonsils, this reflects the condition one month after the demonstration of the vestibulo-ocular disorders.

But definite signs of downward displacement of the midline structures through the tentorial incisura were found in the phlebograms. Also, at the time of the vestibular 'stimulation', the patient displayed signs of disordered circulation, which are generally taken as an indication of displacement, through the foramen magnum, of the medulla; namely a rise in arterial pressure together with a slowing of the pulse rate. These changes occurred *pari passu* with increasing disorders in wakefulness; and the two sets of organismal changes were reversible, in that the administration of hypertonic glucose solution intravenously resulted in their rapid though transient disappearance. The effect of hypertonic glucose injection upon the abnormal intracranial conditions is a sudden diminution of the mass of the entire intracranial content, rather than a direct lowering of the intracranial pressure. A large amount of fluid suddenly passes from the brain substance into the

vessels. The immediate consequence of the changes in mass is a lessening of the displacement of the brain stem. The reflexly elicited arterial pressor response and vagal stimulation are abolished, and the intracranial pressure, which is in part dependent on the arterial pressure, is consequently and mediately lowered (*Ryder* and others (6, 7); *Ewans* and others (8); *Rüshede* and *Ethelberg* (9)).

In supratentorial space-taking lesions, the sites of the severest affection by notching of the midbrain are the cerebral peduncle and the region just below the inferior colliculi. The mode of affection of the neuronal elements may be either immediate by shear-strains, or mediate by impediment of arterial and venous circulation in the structures affected. This may result in oedematous changes, which, naturally, need not be confined strictly to the principal sites of lesion. In the case of severe herniation we are probably concerned with a combination of the two factors.

Now, let us turn to the vestibulo-ocular disorders. The cold caloric 'stimulation' of the ear was in the present case performed with the patient in the recumbent position with the head tilted a little upwards: that is to say, the horizontal semicircular canals were affected. Under cold caloric 'stimulation' the normal vestibulo-ocular reflex is constituted of a slow conjugate deviation of the eyes towards the irrigated side, and a rapid nystagmus movement towards the opposite side.

In the present case the disorders are characterized by severe disturbance of the nystagmus. Nystagmus was either entirely absent, or only transiently present. When present it had the appearance of a rather slow conjugate movement; brisk and rapid jerks were never observed. But the 'tonic' conjugate deviation of the eyes towards the irrigated ear was also disordered in that the latency period was at times markedly increased; there was a marked variation in the intensity of contraction of the medial and lateral recti, in that the adduction was usually more marked than was the abduction; that is, the reversed condition, as it were, of ophthalmoplegia internuclearis anterior; a maximum contraction was at times delayed; inappropriate responses were observed in the nature of by-contraction of non-synergists, such as downward movement of the adducted eye, of convergence reactions and of complete reversal of the 'tonic' response. Also, complete absence of a response was observed.

In the attempt to explain the said disorders, which, certainly, are indicative of marked neuronal dysfunction of the vestibulo-ocular transmission, we must have recourse to the experimental observations of *Lorente de Nó* and to some recent contributions to this intricate question made by *Szentágothai* and *Gernandt*.

As for the nature, in these circumstances, of labyrinthine affection, namely under cold caloric 'stimulation', the original views of *Ewald* (10) and *Bárány* (11) have been corroborated by *Szentágothai* (12) and *Gernandt* (13). The cold caloric affection of the labyrinth will lead to an ampullofugal endolymph current; that is, an inappropriate current as far as the horizontal canals are concerned. This was found by *Gernandt* to be followed in the majority of cases by a decrease in or inhibition of the neuronal activity in the vestibular nerve. This writer also found evidence in a few instances of a direct paralytic effect of cold on the nervous elements; a reaction that may come to interfere with the indirect effect elicited by endolymph current. Whether, under ice water 'stimulation', the paralytic effect may become even more marked remains so far a moot question. If this be the case, one should expect the appearance of conjugate movements of the eyes, that were independent of the position of the head, as this has been observed by *Spiegel* and *Aronson* (14) under continuous caloric stimulation. In one instance the present writer found, in a healthy young man, a positional shift of the nystagmus after irrigation of the ear with 50 ml. ice water (2 centigrades), as should be expected according to the endolymph current theory.

The fact remains, however, that the effect of cold is a decrease in or an inhibition of the impulse activity in the corresponding vestibular nerve, be it in the nature of direct paralysis or of withdrawal of peripheral stimuli.

On the basis of anatomical investigations *Szentágothai* (15) took the view that the elementary vestibulo-ocular reflex arc was a three-neuron arc, connecting directly one crista with two of the extraocular muscles. As for the crista of the horizontal canal these muscles were the contralateral lateral rectus and the ipsilateral medial rectus. This view would seem to be corroborated by observations made by the same writer (12) in experimental animals in which artificial endolymph currents were produced. The internuclear path of the elementary reflex arc is localized in the posterior longitudinal bundle. The intactness of this structure was taken to be a necessary condition for the appearance of 'tonic' (monophasic) contractive responses of a given pair of muscles. Upon this elementary reflex arc multineuronal internuclear chains are superimposed, running in the main through the reticular formation (*Lorente de Nó* 16, 17, 18). The inhibitory impulses are principally mediated by these chains (cf. also 12). The nystagmus elicited under caloric nystagmus, be it cold or hot, is taken by *Lorente de Nó* (*loc. cit.*) to require a certain strength of the stream of vestibular impulses, and, also, the intactness of the reticular formation. At a

certain stage the vestibular impulses will also activate neurons in the reticular formation, setting up impulses, in certain types of self-sustaining chains, that will interrupt the discharges of the motor neurons. Destruction of the reticular formation, and of this only, will result in a monophasic ('tonic') reflex, in which the muscular contraction will last as long as the peripheral stimulus lasts.

This is the type of response we have described as a lasting maximum deviation of the eyes towards the irrigated ear, in the present condition, occurring in the absence of nystagmus.

Under stimulation with inappropriate artificial endolymph current, *Szentágothai* (12) described either complete absence of response, or under certain circumstances, inhibition of existing activity in the set of relevant muscles. Also, under appropriate stimulation, inappropriate reactions were at times noted. Such reactions would seem to imply an abnormal activation of multineuronal chains.

On the basis of the above considerations the vestibulo-ocular reflex changes under cold affection of the horizontal canal must be taken to be the resultant of inconstant inhibitory impulses from the affected labyrinth and the spontaneous activity of the contralateral labyrinth, which latter may be markedly modified by gross affection of the simple and complex internuclear conducting paths.

If, briefly, the disorders of the present cases are reviewed, there are, first, the changes in nystagmus. Commonly, the nystagmus was entirely absent, and when making its appearance, the nystagmus jerks were slow; also, its appearance was a late (delayed) occurrence, it being only transiently present in the course of a test. All these factors point to an interference with the impulse transmission in the multineuronal chains in the brain stem, that is, in the reticular formation, even though the transmission in this structure is not abolished.

Next, since adduction movements were in the main unimpaired, it would seem reasonable to infer that no interruption existed of the impulse transmission through the elementary reflex arc, more particularly through the posterior longitudinal bundle. When in a series of instances the latency period for a response was markedly increased, or a maximum monophasic response was delayed, and when inhibition of the lateral rectus, associated with hypercontraction of the non-synergic medial rectus (convergence reaction) and of the inferior rectus occurred as late phenomena in a test, this would seem to imply recruitment and, consequently, transmission through multineuronal chains in the reticular formation. In the absence of nystagmus these impulses will interfere with the expected monophasic conjugate deviation. On the basis of *Szentágothai's* assumption the occurrence of such hy-

contraction must be taken as an involvement of multineuronal chains since no elementary three-neuron connexions are established with these muscles.

The reversal of the response would seem to depend on the rate of vestibular impulses and the state of contraction of the muscles stimulated. The possibility should be present, under the abnormal conditions, for an impulse to result in inhibition of the set of muscles 'stimulated', leading either to complete absence of a response or to reversal of the response. It would seem ungrounded to assume a direct affection of the abducens nucleus in the explanation of the varying intensity of contraction of the medial and lateral recti, since this disorder was also disclosed after administration of hypertonic glucose. Also, in this case inhibitory impulses through multineuronal chains is the more probable explanation.

Thus, as distinct from the cases reported by *Ethelberg* and *Vernet* (4) of affection by transtentorial herniation of the posterior longitudinal bundle, the vestibulo-ocular disorders of the case here reported seem to be more reasonably explained by taking the secondary affection of the brain stem as leading to marked dysfunction of the impulse transmission in the reticular formation, in the absence of definite signs of lesion of the posterior longitudinal fasciculus.

SUMMARY

A case of purely supratentorial metastatic tumour is described in which angiographical, clinical, and to some degree pathoanatomical changes indicated a severe transtentorial herniation of the midbrain and a foraminal impaction of the medulla. As an additional sign of brain stem affection, a number of varying changes in the vestibulo-ocular reflex elicited under cold caloric stimulation were noted. Their relationship to the process of herniation is discussed, together with the probable basis of their occurrence. It is tentatively concluded that the vestibulo-ocular reflex disorders ensue upon marked disorders in impulse transmission through the reticular formation rather than upon lesion of the posterior longitudinal fasciculus.

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THE SO-CALLED LIPIDOSES.
THEIR HISTOPATHOLOGY AND CHEMISTRY
with special reference to a case of amaurotic idiocy

By

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During the last decades an increasing interest has developed among neurologists in the diseases of the so-called lipidosis-group. In Lisbon in 1953, at the International Congress of Neurology, the lipidoses were one of the main groups debated under the heading of "the metabolic diseases of the central nervous system." Generally speaking the lipidoses were considered to be caused by a disturbance in the lipid metabolism.

However, the possibility of a disturbance in the protein metabolism is to be considered, too. The present paper deals with certain aspects of this hypothesis.

CASE HISTORY

A girl of 13 years was admitted to the Neurological Department of the Municipal Hospital in Copenhagen in March 1954. Her mother suffered from epilepsy during her childhood. The father of the patient's mother was normal, but several members of his family were oligophrenics. The patient's mother had suffered from chorea minor, her brother died in Flensburg (Germany) from some unknown disease with muscular wasting in the legs. Another brother died 10 years old from pulmonary tuberculosis. *Our patient* had 3 brothers, all normal, but a 10 year older sister had suffered from a disease reminding of the present case history. This sister was normal until she was 9 years old. A progressive disease then developed, beginning with epilepsy, mental deterioration and visual symptoms, characterized by a heredo-degeneratio maculae luteae. She died in the hospital for epileptics, Filadelfia, 17 years old. The microscopical diagnosis of the brain changes was: Meningo-Encephalitis basalis et Ependymitis granularis incipiens Ventriculi tertii. However, the description of the brain changes seems to indicate that she had suffered from amaurotic idiocy. In the cortex many ganglion cells were affected, particularly the larger ones, their nuclei being displaced to the periphery by heavy amounts of lipofuchsin pigment.

Our patient progressed normally until her 9th year. The symptoms now began with visual symptoms. She was unable to follow normal school teaching, but was transferred to an asylum for blind persons. During the following years a mental deterioration commenced, and during the following period had retrogressed to such an extent that she was unable to learn anything at all.

On examination she was found to be normally developed, a little fat with an expressionless face. No neurological abnormalities were recorded except for her appearance and gait. She looked like a Parkinsonian patient, walked stiffly with her arms semiflexed and with short steps. Her intelligence was reduced to a stage of oligophrenia. On *ophthalmological examination* a typical retinitis pigmentosa was recorded, but no optic atrophy. Her vision was reduced to seeing "hand movements" on the right, 0.5/36 on the left eye. *Electroencephalography*: Bipolar technique: No focal abnormalities. Monopolar technique: 8 per second activity of medium voltage. In both frontal and temporal areas, left more than right, some interspersed 4 per second frequencies. Further, high voltage 3 to 4 per second runs, sometimes with hypersynchrony and spikes. Such low frequencies appear in periods as paroxysmal discharges. Some solitary spikes over both hemispheres. Conclusion: Bilateral paroxysmal abnormalities consistent with a diagnosis of epilepsy (sign. K. G. Bentsen).

X-ray of the skull, air-encephalography, and the spinal fluid were all normal.

Biopsies from the cerebral cortex and the liver showed the following changes (described by G. Vraa-Jensen):

Cortex cerebri: The ganglion cells enlarged, ballooned, the nuclei lay eccentrically, displaced towards the periphery. The content of the Nissl-substance, stained with the galloxyanin-chromalun method (*Einarsson*), had disappeared, a bee-hive configuration of the cytoplasm was evident. A moderate astroglial proliferation was seen. The tissue from the biopsy was reduced to small pieces; a detailed analysis therefore failed. Diagnosis: Amaurotic idiocy.

The liver: Several small pieces, 12×1.5 mm, show a normal lobulus. No infiltrations around the bile ducts. The liver cells are all big, clear with normal nuclei, foamy cytoplasm and a sharp, dense cytolemma. No pigment was found. The Kupffer cells were normal, some with an eosinophilic cytoplasm. Single eosinophiles were seen among the trabecules. Staining with the galloxyanin chromalun revealed a pathological fainting of the cytoplasm in the liver cells, which were compared with several specimens from normal liver biopsies. Microscopical diagnosis: Degeneratio parenchymatosa hepatis diffusa l.gr.; eosinophilia hepatis l.gr.; decreased basophilia of the liver parenchyma.

Serological examinations: Blood from the vena jugularis, arteria pulmonalis, vena hepatica, vena renalis and from arteria femoralis was taken through a heart-catheterization procedure¹. All these samples were analysed for the content of total lipids, phosphorus-lipid, neutral fat, total cholesterol, free cholesterol, amino-N and glucose. All samples showed identical and normal values. A fractionated analysis of the blood-proteins from venous blood showed normal values, too.

The Takata-Ara test and the thymol test were both normal.

A test for the *hippuric acid synthesis* in the liver showed a decrease to 34.9 % (normal values: 85–110 %).

¹ We are grateful to Dr. *Tybjerg-Hansen*, the Cardiological Lab., Rigshospitalet, Copenhagen, for his kind assistance and interest in the present case. Dr. Tybjerg-Hansen has performed the heart catheterization.

DISCUSSION

In modern medicine amaurotic idiocy is considered part of the greater lipidosis-group. The definition of this group is not quite clear, different diseases being considered members of the group by different authors, but all agree about the following four diseases as belonging to the lipidosis-group: amaurotic idiocy, Niemann-Pick's disease, Gaucher's disease and eosinophilic granulomatosis. The common denominator is the abnormal quantities of lipids in cells.

TABLE 1
Amaurotic Idiocy.

Type	Age at first sympt.	Duration	Clinical symptoms	Retinal changes	Neuro-pathology
Infantile <i>Tay-Sachs</i>	6 months	6 months	Mental dérouté Hypotonia Progressive decerebration	»Cherry red spot«	Diffuse
Late-infantile <i>Dollinger-Bielschowsky</i>	4 years	4 years	The same, perhaps myoclonus-epil.	The same or optic atrophy	Diffuse or disseminated
Juvenile <i>Spielmeyer-Vogt</i>	7 years	10-12 years	Mental dérouté Epilepsy Extrapyramidal sympt. (1) hypokinetic (2) hyperkinetic athetose-torsion-spasms	Optic atrophy perhaps retinitis pigmentosa	Disseminated (1) cortex's deeper layer (2) neostriatum (3) cerebellar cortex
<i>v. Bogaert</i> <i>Jervis</i>			Spino-cerebellar Paraplegia spastica	0 0	
Adults <i>Kufs</i>	3 years	Many years	Extra-pyramidal-Pyramidal-Spino-cerebellar-Ponto-cerebellar Combined Late mental dérouté	0	Cortex Brain stem Basal ganglia Cerebellum Spinal cord.

In Table 1 the different forms of amaurotic idiocy are recorded. It is evident that the border lines between these forms are not sharp and clear-cut. In small children the diffuse changes in the central nervous system correspond to the heavy symptoms representing a slowly progressive decerebration, beginning with cortical symptoms, mental deterioration, petit mal, grand mal, disturbance of vision, motor symptoms ending in a state of decerebrate rigidity. The second group,

Dollinger-Bielschowsky's disease in children about four years old, show more wide-spread and disseminated changes, but little by little these changes get more diffuse. *Haddenbrock* (1950) has found only 12 cases of well-defined late-infantile am. idiocy described in the literature. The disseminated changes only refer to the changes in the white substance, the changes in the ganglion cells are still diffuse.

The third form, the juvenile *Spielmeyer-Vogt's* disease, is the commonest form and the one best analysed. One author alone, *Sjögren* in 1929, has investigated 115 cases of this type from one country (Sweden). This form is the only type in which heredity has been proved to play a role. Family cases are frequent in all forms, but *Sjögren* proved that a recessive factor is present in these families. The clinical type was very uniform in all the 115 cases described by *Sjögren*, characterized by mental deterioration, epilepsy, optic atrophy with or without retinitis pigmentosa. Our case, published in this article, no doubt belongs to *Sjögren's* type, but several cases from other countries differ from this "classical" type. *v. Bogaert* (1953) calls attention to cases of a hyperkinetic type with athetosis and torsion spasms, described by *van der Scheer* and *Winkler* in 1937, as well as an Italian family described by *Jervis*, where pyramidal symptoms were prominent, and to a type described by himself, the heredo-degenerative spino-cerebellar form.

The localization of the cerebrospinal changes varies in these cases belonging to the juvenile type. The ganglionic change is rather diffuse. The clinical picture reflects the dominating localization. In *Sjögren's* classical type the most intense changes occur in (1) the deeper layers of the cortex, (2) the neostriatum, and (3) the cerebellar cortex (*Sjövall* and *Ericsson* (1933)). *Dide* and *v. Bogaert* (1939) state the cerebellar-pallido-hypothalamic-ruber ganglionic systems to suffer most in hyperkinetic cases and *v. Bogaert* (1953) the spino-cerebellar changes in the spino-cerebellar clinical types.

Several cases of "adult" amaurotic idiocy are on record, this type being named after *Kufs*, who in 1925 described the first cases in adults. *Hallervorden* (1938), *Jervis* (1950), and *Marburg* and *Riese* (1947) have reviewed such cases and contributed with their own families or single cases. No uniformity characterizes these cases as regards to clinical pictures. *Hallervorden* is of opinion that it is more correct to call them "protracted cases", because some have never been normal. In *v. Bogaert* and *Borremann's* case (1937) the patient died 65 years old. The negative criteria are characteristic: no amaurosis and, in some cases, no idiocy. It is evident that the diagnosis of such cases is a diagnosis after autopsy.

In the late cases of amaurotic idiocy the changes in the central nervous system are localized, in some cases extremely so (*Hallervorden*, 1938). The small contribution of cerebellar changes is evident in some cases.

The common denominator in all types is the disease of the ganglion cells in the nervous system. Common in all types are the ballooned ganglion cells with the eccentric nucleus, the cytoplasm distended by a substance named "praelipoid" substance, a designation which ought to be abandoned, because nobody knows if this substance represents a stage of assimilation or dissimilation of lipids in the cells. This substance is characterized by staining with Weigert's haematoxylin and a pink tone with neutral fat staining methods. The anatomy of this disease has been extensively studied by several authors (*Schaffer* (1922), *Marinesco* (1925), *Spielmeyer* (1929), *Sjövall* and *Ericsson* (1933), *Bielschowsky* (1936), and many others). The changes involve the ganglion cells as well as the glia cells. The glia cells show the same lipids in their cytoplasm as the ganglion cells, but in several cases the staining shows more neutral fat-like staining substance in the glia cells. The pink tone is approaching more to the normal neutral fat staining. Many authors agree that the change in the neuroglia is coordinated with the change of the ganglion cells, or that even more degeneration is evident in the glia substance. This fact goes against a secondary, only resorptive function of the neuroglia in this disease. Inflammatory changes are never seen.

TABLE 2
Morbus Niemann-Pick.

Age	Clinical Symptoms	Neuropathology
First 2 years of life	Hepato-splenomegaly Skin-changes Gastro-intestinal-sympt. Mental dérouté Physical » Changes in muscular tonus Nystagmus »Cherry red spot«	Changes as in the infantile type of amaurotic idiocy. Foam cells in all organs. The cells of reticular, histiocytotic, and mesenchymal character.
Adults (very few cases)	Hepato-Splenomegaly Hyperlipaemia?	None

Much interest has been devoted to the question about the relations between amaurotic idiocy and Niemann-Pick's disease. Niemann-Pick's disease strikes small children below the second year (Table 2). *Videbæk*

in 1949 collected all the published cases from the literature, contributing with his own cases. The total number is 73 cases. The disease is characterized by spleno-hepatomegaly, a lymphadenopathy, progressive dystrophy terminating in emaciation. In 20 % an increase in the muscle tone is found, in 12 % nystagmus. 20 out of 33 examined patients had a "cherry red spot". Familiarity has been found in 30 % mostly Jewish girls.

In 1937 *v. Bogaert* described one family with a case of amaurotic idiocy and another case suffering from Niemann-Pick's disease. In Lisbon *v. Bogaert* in 1953 discussed this problem. He mentions that in 11 families, representing 22 cases of amaurotic idiocy, only one family suffered from cases even of Niemann-Pick's disease (2 cases), and he refers to *Jervis*, who only found one case of Niemann-Pick's disease among 12 amaurotic idiots. These are small figures, but it must be remembered that Niemann-Pick's disease is only represented by 73 cases in all, while one man was able to collect 115 cases of one type of amaurotic idiocy from one country.

In his paper *v. Bogaert* reports pathologico-anatomical investigations

TABLE 3
Morbus Gaucher.

Type	Frequency	Age at onset	Clinical symptoms	Neuropathology
Infantile acute and subacute	About 35 cases	< 6 months > 6 months	Hepato-splenomegaly 75% central nerv. syst. Mental dêroute Progressive decerebrat. Cranial-nerve-sympt.	Cortical changes, reminding of amaurotic idiocy
Juvenile	3 cases	7 years 3 » 3 »	Hepato-splenomegaly Mental dêroute Epilepsy Extra-pyramidal sympt. perh. pyramidal sympt.	Like amaurotic idiocy The staining is more variable than in the adult cases of mb. Gaucher
Adult cases with central nervous symptoms	4		Hepato-splenomegaly In 2 cases extrapyramidal symptoms In 2 cases symptoms from the hypothalamus and hypophysis	»Balloned ganglion-cells« in the basal ganglia Foam-cells in the spinal cord and radices Changes in the hypophys.-hypothalamic region

of 8 cases of amaurotic idiocy without any evidence of visceral lipidosis, but *Sjövall* (1935) in 21 cases from *Sjögren's* material and in many cases of living patients from the same material in biopsy studies investigated the organs and stated that in all cases a pathological lipid infiltration was demonstrated in the spleen and the lymphatic, axillary, and inguinal glands, and the lipid stored in the sinus cells had the typical pink tone with neutral fat stainings. *Sjövall* concludes that in juvenile amaurotic idiocy an abnormal "Speicherung" exists in ganglionic and glia cells, spleen, and lymphatic glands, signs of an abnormal lipid metabolism. This statement closely connects amaurotic idiocy not only with Niemann-Pick's disease, but also with Gaucher's disease.

Gaucher's disease is defined by *Thannhausser* as a familial disease of the cellular metabolism in the hemato-lymphopoietic organs, clinically characterized by hepato-splenomegaly, blood-changes, anemia, leucopenia, thrombopenia and characteristic changes of the bone marrow, especially in the distal end of the femur. Table 3 shows that any age may be involved, but in children an infantile and a juvenile type may be isolated, and in these small children characteristic central nervous involvement is found. These nervous changes remind of the changes in amaurotic idiocy. Gaucher cells are never demonstrated in the central nervous system. The stainability of the lipids in the ganglion cells varies more than in the older Gaucher patients. In older patients only a few cases show central nervous involvement. In two cases the changes were seen in the hypophysis-hypothalamic region. *Teilum* (1944) considers the microglia cell as the Gaucher cell in the central nervous system. In 2 cases extrapyramidal involvement was evident, but only one case was examined post mortem (*Davidson* (1942)-cited from *Bird* (1948)). In this case a ballooning of the ganglion cells of the basal ganglia was evident. The cells of the putamen and caudate nuclei disclosed loss of Nissl substance. Swelling of their bodies and displacement of the nucleus to the periphery was seen. In the spinal cord large foam cells containing a pale cytoplasm and an irregularly shaped nucleus placed at the periphery were seen, even in the anterior and posterior roots.

In Gaucher's disease, in Niemann-Pick's disease, and in amaurotic idiocy the principle concerning the localization of the abnormal tissue seems to be the same: In small children a diffuse localization is dominating the picture, in amaurotic idiocy only modest, but microscopically verifiable changes in the spleen and the lymphatic system, and with advancing age a more localizing tendency is evident. In Niemann-Pick's disease a few cases in adults have been reported (*Pfändler*

TABLE 4
Eosinophilic Granulomatosis.

Type	Age	Organs involved	Clinical symptoms	Neuropathology
Infantile- <i>Letterer-Siwe's</i> disease	< 2 years	Skin, brain, meninges, osseous syst. lung, pleura, pericardium, lymphatic glands spleen, liver	Poly-symptomatic, lymphadenopathy, petechial skin changes, perhaps hepato-spleno- megaly Triple sympt. (see below)	Diffuse, un- specific, in the brain
Morb. <i>Hand- Christian- Schüller</i>	> 2 years	The cranium, perhaps in other organs	The triple-symptoms: Diabetes insipidus Exophthalmus »Landkartenkranium«	0
Eosinophilic Granuloma	Adults	The same perhaps the cen- tral nerv. system	Disseminated sclerosis Diabetes insipidus Osseous changes	Encephalomy- elitic foci with or without mesodermal changes
Morb. <i>v. Bo- gaert-Scherer</i>	Adults	Cranium Central nervous system Skin tendons	Encephalomyelitis diss. Cholesterol-cataract Xanthelasmata tuberosa, espec. of the Achilleus tendons	Encephalomy- elitis dissem. with or with- out mesoder- mal changes. Cholesterol cryst.

(1946)), without central nervous involvement, the symptoms being restricted to the liver, spleen and lymphatic system.

The same principle holds true in the fourth member of the lipidosis-family, eosinophilic granulomatosis. Table 4 shows the diffuse symptoms and pathologico-anatomical changes in the acute type in small children, the *Letterer-Siwe's* disease. In older children the classical *Hand-Schüller-Christian* syndrome is found with the well-known triad: diabetes insipidus, exophthalmus and the osseous changes in the cranium, evident in X-ray films ("Landkartenkranium"). The clinical picture shows hepato-splenomegaly, lymphadenopathy, fever, skin eruptions, anemia, and pulmonary complications, ending in death in the *Letterer-Siwe's* disease. In the *Hand-Schüller-Christian* syndrome the course is more benign and in adults the characteristic eosinophilic granuloma is seen, with or without partial symptoms from the triad in *Hand-Schüller-Christian's* disease. The prognosis is often good.

Central nervous involvement has been proved to occur in some cases of eosinophilic granulomatosis in adults. The clinical course is very characteristic and reminds of a severe case of disseminated encephalomyelitis of the steadily progressive type, i.e. without remissions. The pathological picture shows changes in every respect reminding of disseminated sclerosis except for a tendency in most, but not all, cases towards an additional mesodermal fibrosis which is unknown in multiple sclerosis. Some cases are on record in which this mesodermal change is not present. At the international congress in neurology in Lisbon in 1953 *Giampalmo* gave a comprehensive exposé of these cases.

A special type of "cholesterol xanthomatosis" has been described by *v. Bogaert* and *Scherer* (1937). The clinical symptoms were: ataxia, symptoms of muscle-tone involvement with hypertonia, bulbar symptoms, and symmetrical tuberous xanthelasmata of the Achilles tendons. A picture reminding of the changes mentioned above, without mesodermal fibrosis, was found together with intense accumulation of cholesterol in the central nervous system. The disease was considered as a disease *sui generis*, but in 1949 *Cureton* described a case with the same changes, but with the mesodermal fibrosis characteristic of eosinophilic granulomatosis.

The cause of eosinophilic granulomatosis is obscure. *Letterer* (1936-38) considers the disease an inflammatory disease, different from neoplastic reticulo-sarcomatosis. Analogies may be found between these changes and *Boeck's* sarcoid.

The common denominator of all the diseases mentioned is the abnormal quantities of lipid substance in the cells. "Lipoidspeicherung" seems no adequate description of what really happens to the tissues, because the endothelial cells of the vessels and the Kuppfer-cells in the liver never show evidence of phagocytosis, except in cases of Niemann-Pick's disease. No abnormal quantities of lipids are found in the blood, except in some cases of Niemann-Pick's disease. In our case even samples of blood from the different organs *in vivo* showed normal lipid-concentrations.

Before proceeding to the lipids involved in these diseases a short review of modern knowledge of the lipids in the central nervous system seems necessary (Table 5).

Fat absorption and intermediary metabolism.

The theory of *Frazer* and coworkers suggests that most fat enters the intestinal cells in an unhydrolysed form finely emulsified as a monoglyceride-bile salt-fatty acid complex. However, some part of the

Neutral fat (glycerol esters)

Lipids of the human brain

<i>Neutral fat (glycerol esters)</i>		<i>Lipids of the human brain</i>	
<i>Phosphatides</i> (Nitrogen and phosphorus-containing lipids)	Monaminophosphatides (ratio of phosphatides to nitrogen 1:2)	Cephalin (choline- phosphoric esters of glycerides)	Phosphatidylethanol- amine Phosphatidylserine Inositolphosphatides
	Diaminophosphatides (ratio of phosphatides to nitrogen 1:2)	Lecithin (choline- phosphoric esters of glycerides)	
	Plasmalogen (acetals of fatty aldehydes with choline glycerophosphate)	Sphingomyelin (contains the amino-alcohol sphingosin and choline)	
	(Phosphatidic acids, resemble monoamino- phosphatides, but absence of nitrogen)		
<i>Cerebrosides</i> (sphingosin, bound to a high fatty acid in acid-amide linkage + galactose)			
<i>Gangliosides</i> (contain neuraminic acid, galactose, and cerebroside)			
<i>Strandine</i> (exact structure unknown)			
<i>Cholesterol</i> { Free Esters			

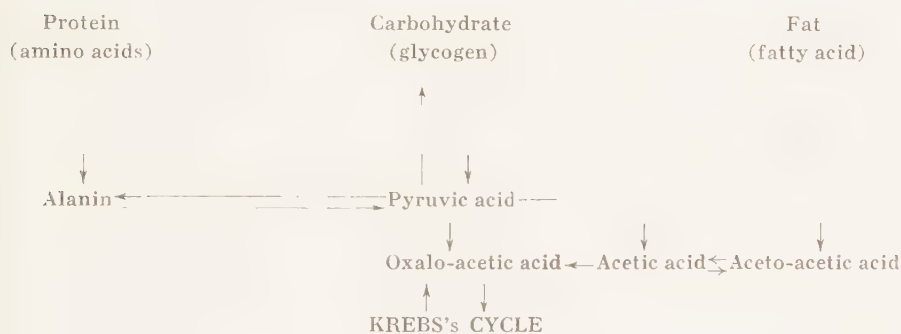
TABLE 5

fat is absorbed as fatty acids. Glycerylphosphoryletholine has been demonstrated in the intestinal mucosa, perhaps being an acceptor of fatty acids.

The deposition and reabsorption of fat from the tissue are influenced by enzymatic processes controlled by the endocrine and nervous systems of the organism. Little is known about these processes.

According to *Knoop* the disintegration of the fatty acids is explained by a successive beta-oxidation, e.g. a splitting off of the final CH_2COOH from the beta-hydroxy-fatty acids forming acetic acid. It was generally assumed that acetic acid then was oxidized to CO_2 and H_2O , but it is now believed that synthesis of aceto-acetic acid is a step in the disintegration of fatty acids.

Lipid metabolism is closely related to protein and carbohydrate metabolism via Krebs's cycle:



Gross composition of the human brain (Sloane-Stanley)
(concentrations as percentage of dry weight: except water)

	Frontal cortex	Corona radiata	Whole brain
Water (% fresh wt)	84.12	69.83	76.9
Protein	44.5	25.2	37.7
Lipid	32.0	57.3	54.4
Extractives	23.5	17.5	7.9

Human brain lipids as percentages of dry weight (Johnson et al.)

	Grey matter		White matter	
	Infant	Adult	Infant	Adult
Cerebroside	5.64	5.54	6.21	16.28
Cholesterol (Total and free) {	5.09	6.28	7.0	14.33
	5.03	6.17	6.70	14.08
Lecithin	7.81	6.25	9.07	4.63
Sphingomyelin	1.30	3.03	1.40	6.82
Cephalin	10.46	11.71	11.57	12.39

Additional mammalian brain lipids as percentages of dry weight
(Sloane-Stanley)

	Grey matter	White matter
Phosphatidylserine	3.2	7.2
Phosphatidylethanolamine	8.5	5.2
Diphosphoinositide	1.3	1.4
Plasmalogen		2.6
Strandin	4.1	2.15
Sulphatide	1	4
Ganglioside	0.46	0.46 ?

Lipid metabolism in vivo.

Earlier it was suggested that the lipids of the brain only had a structural function.

Investigations with labelled fatty acids clearly indicate that a metabolic activity is going on.

Sperry has summarized the results in this field in the following terms:

- (1) The metabolism of all lipids which have been studied is a great deal faster during the early development of the brain than it is in later life.
- (2) There is a small, but definite turnover of fatty acids in the adult brain.
- (3) The metabolism of the phosphatides, as measured by radioactive phosphorus may be quite rapid, considerably faster than most of the data which have been presented would appear to indicate. The "cephalin" fraction is metabolized faster than the lecithin.
- (4) The metabolism of unsaponifiable lipids is exceedingly slow in the adult brain.
- (5) Fatty acids penetrate into the brain, if at all, at a very slow rate.
- (6) Lipids present in the brain are synthesized there and not transported to the brain from other sources.

Enzyme activity.

We have little exact knowledge of the enzyme activity *in vivo*. There is no evidence of a true lipase activity in the CNS—the "lipases" described by the early workers would now be termed esterases. Lecithinase, sphingomyelinase, and cerebrosidase activity has been demonstrated *in vitro* from brains of animals, and a number of other enzymes are suggested, but facts have not yet been established.

Sloane-Stanley states the rates of hydrolysis of "lipins" in the brain *in vivo* and *in vitro* in μ mol/g fresh tissue/h in the following table:

Substrate	Rate	Author
Intrinsic phospholipin .	{ 1.72	Sperry 1947
	{ 0.333	Tyrrell 1950
Phospholipin <i>in vivo</i> ...	0.33	Dawson & Richter 1950
Lecithin	0.985	King 1931
Lecithin (intrinsic)	0.081	Tyrrell 1950
Cephalin (intrinsic)	0.236	Tyrrell 1950
Diphosphoinositide	47	Sloane-Stanley 1951
Sphingomyelin	0.22	{ Thannhauser & Reichel 1936
Cerebroside	2.35	
Sphingomyelin	0.122	{ Rossi 1935
Lecithin	1.675	

Experiments have shown that lipids depots of the organism are influenced by endocrine and enzymatic regulation, and it is now suggested that a permanent shift of the lipids takes place. Here a distinction should be made between the deposition of lipids in the subcutaneous and mesenchymatous tissues. It is suggested that accumulation of fat in the parenchymatous organs is the result of an abnormal metabolism within the epithelial cells of these organs, while the deposition of fat in the subcutaneous tissues may be a physiological process.

Biochemistry of Lipidoses

Lipids involved in the various forms of lipidoses

Disease	Lipid involved	Organs affected
Infantile amaurotic idiocy		
(Tay-Sachs)	Ganglioside	brain, retina
Late infantile amaurotic idiocy	Unknown	brain, retina
Juvenile amaurotic idiocy	Unknown	brain, retina, spleen, reticulum cells
Late amaurotic idiocy (Kufs)	Unknown	brain, retina
Niemann-Pick's disease	Sphingomyelin	reticulum cells, liver, spleen, brain
Gaucher's disease (infantile form)	Cerebroside	{ spleen, lymphnodes, os- seous system, liver
Cerebral Cholesterinosis	Cholesterol ester	brain
Schüller-Christian's disease ...	Cholesterol	brain, skin, osseous system, lymph nodes, spleen, liver, lung

No changes of blood lipids have been demonstrated in the various forms of lipoidosis and it must be stated that these diseases are based on an abnormality of lipid metabolism within the neuron cells.

The biochemical mechanism underlying the metabolic aberration of lipids is entirely unknown.

The lipids stored in the cells in Niemann-Pick's and Gaucher's disease are furthermore of an abnormal chemical structure, unlike the lipids found in the normal organism. The sphingomyelin in Niemann-Pick's disease contains only one fatty acid, viz. stearic acid. In the cerebroside of Gaucher's disease the normally found galactose is replaced by glucose. *Thannhauser* supposes that the balance of enzymes, which leads to cerebroside formation or cerebroside disintegration, is disturbed. Normally lignocerylsphingosin combines with cholinphosphoric ester under influence of phosphorycholinesterase to form sphingomyelin. On the other hand, lignocerylsphingosin combines with galactose or glucose to form cerebroside. In the intact organism this process does not lead to considerable amounts of cerebroside in the liver and spleen, but sphingomyelin is found in measurable quantities. As a result of the disturbed enzyme balance in Gaucher's disease cerebroside accumulates in the organs, but the amount of sphingomyelin is within normal limits. Niemann-Pick's and Gaucher's diseases represent examples of *misdirected synthesis*. The ganglioside found in Tay-Sachs' disease, however, is apparently a normal component of the cerebral cortex, and it must be supposed that in this disease a normal metabolite *cannot be utilized* because of a faulty biochemical mechanism.

Chemical findings from brains of various forms of lipidosis

	Niemann-Pick brain mg %	Tay-Sachs brain mg %	Normal brain mg %
<i>Thannhauser:</i>			
Total cholesterol	6.45	9.90	7.3-15.0
Free cholesterol	5.43	4.10	1.3- 4.6
Cholesterol ester	1.02	5.80	6.1-10.3
Total phospholipids	61.0	19.68	25 -30
Sphingomyelin	4.84	7.04	4.5- 7.0
Cephalin			12 -25
Lecithin			4.0- 6.0
	Niemann-Pick brain (mean)	Tay-Sachs brain (mean)	Normal brain (mean)
and from <i>Klenk:</i>			
Sphingomyelin	5.8	0.3	1.3
Cerebroside	0.7	1.5	2.7
Gangliosides	1.5	6.2	0.3

TABLE 6

From these tables (Tables 6 and 7) it seems evident that the lipid fractions examined in the brain from Tay-Sachs' disease are within normal limits except for the values of the gangliosides.

It must be stated that the lipids in brains from Tay-Sachs' disease are different from those of Niemann-Pick's disease, but it is still under discussion whether amounts of sphingomyelin increase in brains from this last mentioned disease.

The last table shows the chemical findings from the spleen, kidney, and liver in Tay-Sachs' disease, as compared with the normal organs from *Thannhausser*:

	Spleen		Kidney		Liver	
	Tay-Sachs	Normal	Tay-Sachs	Normal	Tay-Sachs	Normal
Total cholesterol ...	3.10	1.8- 2.4	2.69	1.4- 2.8	3.78	2.0- 2.6
Free cholesterol	1.36	1.6- 1.1	0.92	1.0- 1.1	0.47	0.4- 0.5
Ester cholesterol ...	1.74	0.7- 1.3	1.77	0.5- 1.7	3.31	1.5- 2.2
Total phospholipids .	8.30	5.5-11.0	9.52	7.0-10.0	9.26	9.0-11.0
Sphingomyelin	1.04	0.7- 1.0	0.80	0.6- 0.8	0.55	0.3- 0.5
Cephalin	4.80	1.5- 7.0	3.95	2.0- 4.0	—	3.0- 5.5
Lecithin	2.46	3.0- 4.0	4.77	4.0- 7.0	8.71	3.0- 6.0
Total fatty acids ...	5.97	4.0- 6.2	10.40	5.5- 6.2	27.4	8.6-13.0

TABLE 7

In the organs of Tay-Sachs' disease no significant variations of the lipid fractions are seen, as compared with normal values. However, the amount of total fatty acids in the kidney and the liver seemed to have increased, the amount being in the liver. At last it should be mentioned that the methods suitable for estimating the various lipid fractions in the organs have not been developed to such a degree that the results are directly comparable from author to author.

Common to all the diseases belonging to the lipidoses is a more diffuse involvement of the central nervous system, and in a certain degree the whole organism, in small children; with increasing age a progressive tendency towards the development of localized lesions seems evident. Eosinophilic granulomatosis seems to be a variant from the other lipidoses regarding changes in the central nervous system as well as the composition of the lipid substance involved. However, the aforementioned general principle of different localization during different ages holds true. In eosinophilic granulomatosis the lipid involved is cholesterol, but in the other three types of disease chemistry and neuropathology are related, as far as is known to-day. The common

denominator is the ballooned ganglion cell, seen in amaurotic idiocy, Niemann-Pick's disease and in Gaucher's disease if there is nervous involvement, and in the chemistry the lipid involved have a common link in the sphingosine-base. In eosinophilic granulomatosis the changes to a considerable degree differ from those in the other members of the lipidosis-group.

What is the essential process underlying this biochemical abnormality resulting in the "ballooned ganglion cell"?

In our case a significant decrease in the chromidial substance in the liver cells appeared as compared with biopsies from normal livers. It is well-known that in the ballooned ganglion cell a decrease to complete disappearance of the chromidial substance is always demonstrable. The involvement of millions of ganglion cells is evident in all cases, but according to *Sjövall* and *Ericsson*, no evidence of cell death is found in the juvenile group. These authors have examined the greatest material of juvenile cases ever published. However, in the infantile group frequent signs of neuronophagia have been observed by many authors.

According to *Globus*, strongly supported by *Bird*, the lipid in the ganglion cells in different cases of lipidosis "are normal constituents of the nerve cells. Only when present in excess do they cause harmful effects, and then mechanically rather than by virtue of their chemical composition." They accumulate and displace the content of the cytoplasm, and at last the cell dies.

During recent years increasing evidence has been collected to prove that the basophil substance of the cytoplasm in all cells contains ribonucleic acid (RNA). According to *Palade* and *Porter* (1952) the chromidial RNA-containing substance forms an endoplasmatic reticle. *Lagerstedt* (1949) has demonstrated the RNA-content of the basophil substance stained by the Gallocyanin-chromalun technique, the same substance staining specifically in the ganglion cells. This chromidial substance is engaged in the continued metabolic processes building up the cytoplasm of the ganglion cells, from which the axon is supplied (*Weiss* and *Hiscoe*, 1948).

Highly active cells contain large amounts of RNA and show a strong basophilia. This shows the basophilia of the active stages of the blood-cell-building reticulum cells and the nerve cells.

The abnormally low basophilia of the liver cells in our case of amaurotic idiocy and the low concentration of the chromidial substance in the ganglionic cells may be correlated. It means perhaps that the activity of the liver regarding protein-synthesis is disturbed and the enormous supply of aminoacids for the building-up of the nervous

chromidial substance is insufficient, or a constitutional disease in the RNA-metabolism is reflected both in the liver cells and the nervous cells.

The RNA-content in the cellular elements is bound to phospholipid components (see *Ham* (1953)). A disturbance in the link between the protein and the phospholipid may contribute to an accumulation of the lipids following this disturbance in the equilibrium of the chemical process.

SUMMARY AND CONCLUSIONS

A case of amaurotic idiocy of the juvenile type is described. Samples of blood from different organs *in vivo* showed a normal content of lipids, amino-N and blood sugar. Biopsy from the liver was compared to biopsies from patients with a normal liver function. A decrease in the basophilia of the liver cells in this case of amaurotic idiocy was demonstrated. A decrease to $\frac{1}{3}$ in the hippuric acid synthesis of the liver was found.

The different diseases belonging to the lipidosis-group are reviewed with special reference to the changes in the central nervous system. It is concluded that the common denominator of amaurotic idiocy, Gaucher's disease, and Niemann-Pick's disease in the central nervous system is the ballooned ganglion cell, filled with a lipid substance belonging to the cerebrosides. The changes are diffuse and most prominent in small children during the first years of life. In eosinophilic granulomatosis other changes in the central nervous system are found and the lipid involved is cholesterol.

The chemistry of the lipids in the central nervous system is reviewed with special reference to the lipidoses.

The decrease in the basophilia of the liver in our case is correlated to the decreased basophilia of the nervous cells in cases of lipidosis.

The hypothesis is proposed that the decrease in the basophilia of the liver is an important change in the cytoplasmatic metabolism pointing to a disturbance in the supply of the nervous elements for amino-acids, necessary in the synthesis of the ribo-nucleic acid, or a constitutional abnormality in the ribo-nucleic acid metabolism in the whole organism is reflected in the decreased basophilia in both the liver and the nervous system.

It may be of some importance that the organs in strong activity, especially the blood-building organs, suffer most in the diseases belonging to the lipidosis-group, and that the nervous system suffers most during the first years of life, in which the need for ribo-nucleic acid is specially high during the growth of the neurones.

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A SURVEY OF METHODS FOR THE DETERMINATION OF THE PROTEIN FRACTIONS IN THE CEREBROSPINAL FLUID

By

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Exact quantitative determination of the protein content in the cerebrospinal fluid for clinical purposes has always caused difficulties, and the problem has hardly been definitely solved yet. This, of course, applies to a still higher degree to determinations of the separate protein fractions. Nevertheless such investigations were attempted at a very early date.

As early as 1909 *Ross and Jones* (26) described a method by which a surface reaction to saturated ammonium sulphate solution was used to express the globulin content in the cerebrospinal fluid (CSF). A modification of this test was included in *Bisgaard's* method (3) as a measure of the so-called globulin figure, and is thus still used in several places, at least in this country (21), though its value has been much questioned by several authors (14, 33).

Determination of the albumin-globulin quotient in plasma has been carried through as a clinical method, and has proved to be of great practical diagnostic importance, whereas similar determinations in the CSF have met with great difficulties. These are due to the following facts: The protein content in the CSF is very low as compared with that of the blood, and generally only relatively small portions of CSF can be procured. If we take it that a normal CSF contains 0.04 per cent of protein at the utmost, and if we have 15 ml for the analysis, only 6 mg of protein are thus available. Moreover, a simple Kjeldahl determination is not sufficient to measure the total protein, as the content of non-protein nitrogen is much higher than that of protein nitrogen.

The most accurate method with which to estimate these fractions is presumably that described by *Izikowitz* (14). The special feature of this method is that, after precipitation and centrifugation of the pro-

tein, a destruction is performed at a high temperature in the same tube in which precipitation and centrifugation took place. The nitrogen is then determined by iodometric titration. This is thus a quantitative chemical analysis according to classic methods, determining both the total protein and the globulin, i.e. the proportion of the protein precipitated by semisaturation with ammonium sulphate. *Izikowitz* stated himself that he could determine the protein fractions with a mean error of 1 per cent at the utmost. Other investigators, however, have found that the method is somewhat less accurate. In this country, *Trolle* (31) has re-examined the method and found the mean error of the determinations to be so great that a calculation of the albumin-globulin quotient becomes illusory in the case of a CSF with a low protein content.

Izikowitz's method has not been adopted as a clinical routine method, at least not in Denmark; this is due to the fact that it is technically difficult and rather time-wasting.

A method much used abroad in spinal fluid investigations is *Lange's* gold sol reaction (20), which is one of the so-called colloidal reactions. Another is the mastic test (9). These methods rest on a purely empirical foundation. Although they afford no direct expression of the occurrence of the separate protein fractions, the results are presumably to an essential degree dependent on the quantitative relationship between these (22, 25). With the gold sol reaction a special colloidal gold salt solution is added to a number of different dilutions of the CSF in ten tubes. Any precipitation in the various tubes is observed, and its degree is expressed by the figures 0 to 5. The reaction can be recorded by a series of figures or by a curve, as, for instance, in the *Takala* test.

In 1946 *Scheid* and *Scheid* (28) made an attempt to investigate the mastic test by applying it to electrophoretically isolated plasma fractions. The characteristic mastic curve was found for the separate fractions and for definite mixtures of the fractions. The authors stated that on the basis of the mastic curves obtained with CSF they were able to give some estimate of the content of, for instance, albumin and γ -globulin.

The development during recent years in the investigations of the serum proteins, especially the increasing use of physico-chemical methods, is also reflected in the spinal fluid investigations. However, difficulties have also been met with here because of the above-mentioned peculiarities in the composition of the CSF. It is especially the electrophoretic separation of the protein fractions that has been used also in examinations of the CSF.

Owing to the low protein content in the CSF it is desirable in electrophoretic investigations to bring the protein content up to about 1 per cent by preceding concentration. For this purpose methods of precipitation, freeze-drying and dialysis have been used. Such a concentration process is associated with a number of technical difficulties. The concentration is rather prolonged with most of these methods: denaturation or hydrolysis of some of the protein may therefore readily take place, as it is less stable in these weak solutions than, for instance, in plasma. If the concentration process includes dialysis, adsorption to the membrane may cause a loss of protein. To provide against these sources of error, it will be necessary to examine in advance whether the process has caused a loss of protein. Some of the discrepancies between the results of various authors may presumably be explained by the fact that these sources of error have not been considered. A detailed discussion of these problems is to be found in (13).

The electrophoresis apparatus of *Tiselius* was introduced in 1937. Already in 1939 *Hesseltvik* (15) investigated a number of normal and pathological body fluids, pleural fluids, ascites fluid, etc. The material included 2 samples of spinal fluid, both from patients with general paralysis. In both cases the diagram showed an albumin and a γ -globulin peak.

In 1942 *Kabat* and co-workers (16,17) reported the results of electrophoretic investigations of the spinal fluid with the same apparatus. The material was obtained by air encephalography and ventriculography. The portions of CSF were concentrated to a volume of 0.2 ml by pressure dialysis against salt water at $+5^{\circ}\text{C}$. Protein concentrations varying from 0.4 to 1.5 per cent were thus obtained. These solutions were then dialyzed against a buffer solution and examined in the electrophoresis apparatus with a micro-cell. The authors found that the CSF proteins contained the same fractions as plasma. In some cases with an increase of the CSF protein they could demonstrate all plasma protein fractions, whereas in samples of normal CSF they were sometimes unable to demonstrate α -globulin and fibrinogen. The albumin-globulin quotient was often higher in CSF than in serum. In cases with increased total protein the rise was generally due to albumin. In patients with abnormal composition of the plasma protein the authors found in some cases that these changes recurred in the CSF. In patients with infectious disease outside the central nervous system an increase of γ -globulin was found both in the serum and in the CSF. In contrast with this it appeared that patients with neurosyphilis had an increase of γ -globulin in the CSF without a correspond-

ing rise in the blood. The authors therefore concluded that not all protein in CSF originates from the blood.

With regard to the concentration methods employed, the following publications may be mentioned: —

Ewerbeck (11) used two different methods of concentration. In the first, CSF was dialyzed against a concentrated colloidal solution. The osmotic forces will then cause water to pass through the dialysis membrane; owing to this the volume of the spinal fluid will be reduced, whilst at the same time its protein content rises. Concentration by ultrafiltration was used in the second method. In order to control that these methods of concentration did not cause a loss of protein of any significance, model experiments were performed with serum dilutions of a protein content similar to that of the CSF.

Labhart and co-workers (19) concentrated CSF by pressure dialysis against a buffer solution, which was later used in the electrophoresis experiment. This was performed in a special micro-electrophoresis apparatus permitting examination of 0.4 ml of a 1 per cent protein solution. These authors, too, performed control experiments with concentration of serum dilutions, and found good conformity in electrophoresis experiments with the unconcentrated serum. The same authors have performed experiments with another concentration method, namely dialysis with ensuing freeze-drying. With this method, however, the control experiments were not in accord with those on unconcentrated serum.

Esser and co-workers (10) have described a method of simultaneous dialysis against a buffer solution and evaporation in an exsiccator in a special apparatus. A disadvantage of this and of many of the other methods hitherto mentioned is that it requires a certain time, from one to several days, and, as already mentioned, processes of destruction, bacterial decomposition, and the like may then have time to prevail. It has therefore been attempted to elaborate methods requiring less time. *Esser* and co-workers (10), in another publication, have described an apparatus in which ultrafiltration is performed by pressing the CSF through a membrane at a pressure of 12 atmospheres. In this way 5 ml of CSF can be filtered in 6 hours. After filtration the protein lies precipitated on the filter and can then be dissolved in a small quantity of buffer solution. The authors are able clearly to distinguish an albumin and four globulin fractions in the electrophoresis diagrams.

Important new contributions to the elucidation of these problems have been given by *Schneider* and *Wallenius* (29) and *Wallenius* (32). They performed the concentration by dialysis against a 10 to 20 per

per cent dextran solution in a 0.9 per cent saline solution, the CSF sample thus being reduced to quantities from 0.1 to 0.2 ml of concentrate. The further investigation was performed with paper electrophoresis according to methods similar to those used in serum protein investigations. In all cases the authors undertook parallel investigations of CSF and serum from the same patient. The serum and the CSF electrophoresis diagrams showed very close conformity in all normal cases. Thus there was an albumin-globulin quotient of almost the same magnitude in CSF and in serum. The authors pointed out that this was not in accord with the results found in salting-out experiments (*Izikowitz*), where the albumin-globulin quotient was found to be much higher in normal CSF than in serum. In the authors' opinion this is due to the fact that, with the low protein content in normal CSF, the globulin is not precipitated so completely as in similar precipitation experiments with a more concentrated protein solution, e.g. serum. Moreover, the globulin defined by precipitation is not identical with the electrophoretically determined globulin. The authors examined some cases with abnormal composition of the serum proteins, e.g. cases of myeloma and cirrhosis of the liver, without symptoms of disease of the central nervous system. They found changes in the protein fractions of the CSF of exactly the same nature as in the serum. Among patients with diseases of the central nervous system and with increased protein content in the CSF they found some cases in which the protein fractions showed an equal rise (meningitis, tumours) and others in which the diagram differed much from that obtained in the serum protein investigations. In most of the latter cases they found an especially great rise in the γ -globulin content, e.g. in some cases of neurosyphilis and disseminated sclerosis. However, the authors would not give an opinion as to the diagnostic conclusions which may be drawn from the electrophoresis diagram of the CSF.

It may be mentioned that in some patients with Guillain-Barré's disease, *Steger* (30) found a relative γ -globulin rise both in the serum and in the CSF.

In 1953 *Cumings* (7) investigated a number of pathological spinal fluids and cyst fluids with a method similar to that of *Schneider* and *Wallenius*. CSF samples especially from patients with neurosyphilis, disseminated sclerosis, and cerebral tumours were examined, but the electrophoresis diagrams in these diseases differed rather much, even in patients suffering from the same disease. With regard to the diagnostic value of the method, the author therefore arrived at the same conclusion as *Schneider* and *Wallenius*.

The authors hitherto mentioned found only protein fractions in

CSF which were already known from serum, whereas *Fisk* and co-workers in 1951 (12) in all CSF samples examined found a special fraction, termed X, which migrates ahead of the albumin peak. In some cases they also found a smaller fraction, termed X_1 , with a slightly greater rate of migration. X amounted to quantities from 3 to 17 per cent of the total protein, X_1 to about 1 per cent. The fraction X was isolated in an electrophoresis apparatus, and then examined by ultracentrifugation. It appeared to have the same sedimentation constant as serum albumin. Electrophoresis experiments with plasma diluted to the same protein content as the concentrated CSF showed no traces of the components X and X_1 . The authors, however, mentioned that they may have been concealed in the albumin peak, which spreads much under these experimental conditions. Nevertheless the authors consider that X and X_1 are produced in the central nervous system, and that they are characteristic of CSF.

A fraction similar to X was also demonstrated by *Bücher* and co-workers, who termed the fraction V. In addition they found a smaller fraction, termed τ , which travelled close behind β -globulin, and was not demonstrated in plasma. The fact that the authors previously mentioned did not find these "foreign" protein fractions as well, might be thought to be due to their being artificial products formed in the course of the concentration processes. This assumption is contradicted by the fact that uniform fractions of this group could be demonstrated by two groups of authors independent of each other, who used highly different methods of concentration. *Fisk* and co-workers (12) concentrated the CSF by pressure dialysis and ensuing dialysis against phosphate buffer, whereas *Bücher* and co-workers (5, 6) precipitated the proteins with acetone at a low temperature, and redissolved the precipitate in a quantity of liquid which was from 100 to 200 times smaller. Finally, in 1953 *Bauer* (1) mentioned some experiments performed by *Mohring* and *Matzell* in which CSF was concentrated by ultracentrifugation and then examined by electrophoresis. With this method, too, the fractions X, X_1 and τ were demonstrated.

Eaton and *Gardner* (8) used a special method of concentration, in which they first removed the salts of the CSF by making it pass an ion exchanger. It was then freeze-dried, and the dry substance was redissolved in a small quantity of saline solution. Further investigation was performed with paper electrophoresis. These authors could not demonstrate the fractions X and τ mentioned above.

In 1954 *Roboz* and co-workers (24) used paper electrophoresis after concentration of CSF in a manner similar to that used by *Bücher et al.* Readings were taken from the paper strips by a photo-electric

method measuring directly the amount of light passing through a number of points on the dyed paper strip. The authors discussed the sources of error in connection with the dying of the strip. The results of the investigations were only briefly mentioned. In particular it was not stated whether the additional fractions mentioned above could be demonstrated. However, in a few of the diagrams published a component could be seen migrating ahead of the albumin peak.

Besides the electrophoretic method, another of the modern physico-chemical methods of protein analysis, ultracentrifugation, has been used in spinal fluid investigations. In 1954 *Frantzen, Frantzen, Djurkøft and Fog* (13) published some results of ultracentrifugation experiments with concentrated and unconcentrated CSF. In these investigations, too, the quantitative distribution of albumin and globulin was almost the same as in the serum examined at the same time. In other cases, in patients with diseases of the central nervous system, there was a distinct difference between the sedimentation diagrams from CSF and from serum. There was a relative rise in the globulin content in the CSF in such cases.

A special method was used by *Kabat* and co-workers (18). They examined the proteins in the CSF by immuno-chemical methods, preparing antibodies both against albumin and against γ -globulin. Quantitative precipitation of the fractions concerned was then made with these antibodies. The precipitates were washed and then measured by micro-Kjeldahl analysis. Normal values were established for the γ -globulin content in per cent of total protein. It was shown that this fraction may be increased in certain diseases, especially in disseminated sclerosis and neurosyphilis.

Another method of estimating γ -globulin in CSF has been described by *Saifer and Narby* (27). In this method, γ -globulin is precipitated with a special lipid emulsion (deoxycholic acid and cholesterol). After removal of the lipid with ether, the content of protein in the precipitate is determined colorimetrically. The authors found their results to agree with those obtained with *Kabat's* immuno-chemical method, and considered that their procedure could be used as a clinical routine method.

In Denmark, *Claus Munk Plum* and co-workers (23) recently described a method with which to determine both the total protein and the globulin content in CSF. With this—as with *Izikowitz's* method—it is the salted-out globulin that is estimated. The method is based upon the property of protein of combining with a dye just as in the method with which the paper strip is dyed in paper electrophoresis, and the protein fractions are determined quantitatively from the

amount of dye that has been bound. As albumin and globulin bind the dye to a different degree, it is necessary to determine the globulin fraction separately after precipitation by means of semisaturation with ammonium sulphate. The method is much simpler than that of *Izikowitz*.

DISCUSSION

When the historical development of our knowledge of the protein fractions in CSF is studied, it can be said, summarizing, that the question was the subject of investigation at an early date, but that only the progress in protein chemistry during recent years, especially the introduction of the methods of electrophoresis, has caused such investigations to rest on a sufficiently exact foundation.

It must be considered well established that there is a close connection between the proteins in the serum and those in the spinal fluid; for the normal CSF chiefly contains the same protein fractions as are present in serum, and presumably in exactly the same relative proportions. Pathological changes in the serum proteins are also often reflected in the CSF. On the other hand, it must be supposed, as pointed out by *Kabat* (16, 17) and by *Schneider* and *Wallenius* (29) among others, that a local liberation or synthesis of globulin may take place in the central nervous system. It is often the γ -globulin fraction that is increased, and in the case of infectious diseases this rise may presumably be indicative of an antibody-production. In such diseases, *Bing* and *Neel* (2) found an accumulation of plasma cells in the central nervous system and its membranes. This is in accord with the assumption (*Bjorneboe* and *Gormsen* (4)) that these cells are the site of formation of antibodies.

It has not yet been definitely established whether there are protein fractions which are specific of CSF.

The question whether the electrophoresis methods will become of practical diagnostic value in future in this field depends on the possible finding with these methods of sufficiently characteristic changes in the protein fractions of CSF in certain diseases or groups of diseases. Whether this is practicable, cannot be decided on the basis of the literature hitherto published. The different studies have been performed with much varied methods and techniques, and the clinical data in the actual cases examined are generally very few.

It is thus too early to say which methods will be preferred in future. For clinical purposes it may possibly suffice to determine the total protein and, for instance, γ -globulin (18,27). The employment of electrophoresis could thus be avoided, and this method causes special technical difficulties in the case of CSF investigations.

SUMMARY

On the basis of the literature a survey is given of methods of determination of the protein fractions in CSF. The results hitherto obtained and the possible future development are discussed.

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THE DIAGNOSTIC AND THERAPEUTIC VALUE OF NARCOANALYSIS IN A PSYCHIATRIC RECEPTION DEPARTMENT

By

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In 1874 a book by a young philosopher, *Benjamin Blood*, "The anaesthetic revelation and the gist of philosophy," was published in the U.S.A. In this book the author describes his experiences during and after the inhalation of nitrous oxide, which had previously been tested by *Davy* and *Barton*.

Blood writes as follows: "I affirm that there is an invariable and reliable condition . . . ensuing about the instant of recall from anaesthetic stupor to sensible observation, or coming to, in which the genius of being is revealed; but because it cannot be remembered in the normal condition it is lost altogether through the frequency of anaesthetic treatment in any individual's case ordinarily, and buried, amid the hum and returning common sense, under that epitaph of all illuminations: this is a Queer World." This communication inspired *William James* to making similar experiments and gave rise to an age-long correspondence and a lifelong friendship between him and *Blood*.

As far as can be judged, these experiments had no direct influence on the development which led to the use of inhalation of carbon dioxide and narcoanalysis in psychiatry; at any rate they are not mentioned by *A. S. Loewenhardt* and *W. P. Lorentz*, who as early as 1916 began treating a stuporous catatonic with intravenous injections of sodium cyanide. The substance had a stimulating effect on the patient's respiration and brought about a change in his condition. *Lorentz* describes the effect as follows: "This patient had been mute for a long time and presented the typical fixed, rigid attitude so characteristic of this condition. After a period of respiratory stimulation the patient relaxed from the rigidly held posture, the eyes opened, the facial expression

appeared animated and a few intelligible and relevant replies were obtained to our questions.

We were impressed with this interesting response at the time but, owing to our occupation with an important clinical problem, and our later military affiliation, no further investigations were attempted along this line until 1928, at which time we repeated our former experiments and obtained the same results. Upon theoretical grounds, and as a consequence of previous work by Loevenhart, carbon dioxide gas was used to stimulate respiration, and produced, if possible, a psychic response similar to that previously observed with the use of sodium cyanide. It was found that mixtures of carbon dioxide and oxygen under certain conditions, when inhaled, produced the same phenomenon, though more pronounced than that observed with use of sodium cyanide. That is, the mutism and muscular rigidity could be made to disappear by carbon dioxide and oxygen inhalations."

In 1928 *W. J. Bleckwenn* made some experiments with intravenous injection of sodium amytal on psychotic patients, and they responded in a way similar to that described by *Lorenz*. *Bleckwenn's* intention, however, was that of putting the patients into a prolonged state of profound sleep. He then noticed that the patients afterwards were more talkative and more co-operative and accessible to psychotherapy; but he does not mention the use of the method for any proper abreaction of psychotraumatic experiences, as later discussed by *Horsley*.

Six months later *W. Lorenz* and co-workers tried this substance upon stuporous catatonics, who brightened up for six or seven hours, after which they relapsed into their stuporous state.

In 1930 *H. C. Solomon*, *M. R. Kaufman*, and *F. D. Elseaux* published some investigations into the effect of intravenous injections of sodium amytal upon a schizophrenic patient, who likewise brightened up for a short while.

They made another stuporous patient inhale a mixture of 40 per cent. carbon dioxide and 60 per cent. oxygen, after which the patient became attentive and talkative for about half an hour. The last-mentioned experiments became the starting-point of *Meduna's* greatly mentioned and discussed treatment with carbon dioxide.

In Europe narcoanalysis has particularly been known through *J. Stephen Horsley's* works, more especially through his book "Narcoanalysis", which was published in 1931. The word *narcoanalysis* has been coined by him.

The method, indeed, was used somewhat during the following years, but not until World War II was it universally known and used for the abreaction of actual psychotraumatic experiences in soldiers

and civilians who were subject to severe neurotic and psychotic reactions as a consequence of their war experiences. The method yielded excellent results, and it was commonly held that it might also be used under conditions of peace and with as good an effect in the case of psychoneuroses, more especially, of course, the psychogenic ones.

During the post-war period countless works on narcoanalysis, narcohypnosis, and narcosynthesis have been published, in which the tendency is gradually towards greater and greater scepticism as regards the diagnostic importance of the method and its therapeutic value in cases in which there are no comparatively recent and really straining psychogenic factors.

In criminology the method has been used somewhat, especially previously; but it has also been severely criticized from ethical, legal, and medical-psychological points of view.

The question about the reliability of the information offered and statements made by the narcoanalyzed person has also been the object of much discussion.

Narcoanalysis was frequently mentioned in the popular press under the misleading and infelicitous name of *truth serum*; but now it is fairly rarely used, chiefly in connexion with trials behind the iron curtain.

In Western Europe the general standpoint is that the method should only be used on a voluntary basis, and that the information obtained does not in itself carry any weight as evidence.

In time the indications for narcoanalysis have been stricter and stricter, as, indeed, is the usual development when new treatments are taken into use.

Stimulated by the multitude of encouraging results also after the war, narcoanalysis has quite naturally been introduced in the psychiatric departments of hospitals in this country, but so far no general survey of this material is available. I have therefore found that it might be of interest to publish a material from a psychiatric reception department, the staff of which has been particularly interested in psychotherapy. Some of the collaborators have had a supplementary psychoanalytic

TABLE I

	Men	Women	In all
1950	11	10	21
1951	10	18	28
1952	2	18	20
1953	1	4	5
1954	4	2	6
In all	28	52	80

training, others have not; but this fact does seem to have had any influence upon the examination and treatment.

During the years 1950-54 narcoanalysis of a total of 80 patients was made, as appears from Table I.

Thiopentymal or Narcodorm was used in individual doses; otherwise the technique has been the usual one, and there has been no dangerous complications of any kind.

The examinations and the psychotherapy has generally been performed by the assistant physicians or the permanent house physicians. In a single case, only, there was a transitory state of unrest after the examination; but there were never so strong responses that the patients had to be moved from a quiet to an unruly ward, and they soon calmed down again. Nor was any one particularly afraid of the examination, even though perhaps the name of truth serum in a single patient had a slightly deterrent effect; but the patients were always soberly informed of the purpose and possibilities of the examination. Most of them were given a final dose producing a short sleep. Naturally they were all of them interested in the question whether they had said anything which afterwards they could not remember, and they often stated that, indeed, they might have made the same statements when awake, which was no doubt correct in the case of the majority.

If there is a really good contact between patient and physician, it is in my opinion possible from the great majority of patients to obtain as good information without narcoanalysis, as also indicated by the case records and as may be ascertained when one knows the various physicians through collaboration during a lengthy period.

The number of narcoanalyses varied somewhat, but on an average there were two or three and furthermore a number of conversations both before and afterwards. Some psychiatrists may perhaps be of opinion that the analyses ought to have been repeated for a longer time; but personally I do not think that the results would have been different if so, as is also corroborated in the cases in which up to 10 narcoanalyses have been made. The reason why the method has been abandoned in individual cases is that no further information was obtained and there was no abreaction.

As appears from Table I the majority of narcoanalyses were made during the years 1951-53, after which they were practically abandoned.

The explanation of this is presumably that during the three years mentioned there were several of the assistants who were much interested in psychotherapy, but as the whole staff gradually realized that so little was gained by this treatment the interest in it decreased, and the new assistants pursued new courses in therapy. The permanent

figure—the chief physician—also quite naturally lost interest in narco-analysis and finally has practically ceased prescribing this form of examination, respectively treatment. No especially complicated technique has been used at the examinations. The patients were made to talk and some questions were asked in connexion with their statements and on the basis of previous knowledge. Nor has any interpretatory technique on classical psychoanalytical lines been used, but it has been tried to explain to the patient the signification of certain experiences and conditions on the basis of generally recognized psychological points of view. There were no patients who felt annoyed by the examination or found it inhuman, but in many cases they have expressed their disappointment “that this was all”, and that it was no more profitable.

It is inevitable that the selection of the patients must be due to a subjective estimate; but on the whole it was patients with rather bad neurotic disturbances of long standing who were subjected to narco-analysis. An apparently unprovoked, but troublesome fear was a basic symptom in most patients, a symptom which no doubt mainly suggested the use of narcoanalysis.

As the number of patients is rather small, I have found it pointless to go into detail as regards a statistic working up of the material, but I find that it may be of interest to see what has been the result of the work at these patients who undoubtedly were among the worst in the neurotic group, but who on the other hand have been the object of so much interest as can be shown these patients at a psychiatric department.

TABLE II

	Men	Women	In all
Nervous from childhood	16	34	50
Not nervous from childhood ...	12	18	30
In all	28	52	80

Table II indicates something about the premorbid psyche.

The ages of the patients are between 15 and 55 years without any significant distribution to the various age-groups.

Out of the 80 patients there were only 20 who showed some psychological reaction which must be ascribed to the narcoanalysis. Out of these 20 there were only 5 who must be supposed to have benefited by the narcoanalysis, and this is even far from being certain and at any rate cannot be proved.

Unfortunately the majority of the patients had also been given

other forms of treatment, which indeed further detracts from our confidence in the assumption that narcoanalysis as such should have been the decisive factor. I think that the same result within a similar material might have been obtained only by confinement to bed, sedatives, and roborant treatment in connexion, of course, with a similar number of well-prepared conversations. Nor should it be forgotten that the patients are selected for narcoanalysis and that the fact that a physician before and after the analysis devotes some of his time to them may have a certain effect in a positive direction.

So I must already here conclude that narcoanalysis as such had no real diagnostic or therapeutic value for our material, perhaps apart from the five cases which will be briefly mentioned below.

From nine patients new information was obtained, in eight a certain outburst of passion, and ten became more voluble, but it is not possible to point out any actual connexion between e.g. an outburst of passion and the final result or between new information given during the narcoanalysis and the final result; but as mentioned above, the figures are so small that they are insignificant, and the same patient may appear in the various groups of reaction, thus e.g. both show outbursts of passion and give new information. The only thing that may be maintained with certainty is that narcoanalysis was a disappointment both diagnostically and therapeutically, which is no doubt the actual reason why it has been used in so few cases during the last two years.

By a critical evaluation of the new information obtained during the narcoanalysis one arrives at the result that this is of little or no importance and that through some searching conversations without narcoanalysis it would probably still have been obtained, and that the fact that the information was obtained was not tantamount to abreaction and cure. Only in two cases it is possible with a little willingness to find a connexion.

A really actual trauma of pathogenetic importance was found in eight cases only.

The fact that so many of the patients had been nervous from childhood, does not exclude the importance of an actual trauma, on the contrary, one might say; but here it was more difficult to estimate what was really a dynamically actual trauma than in the patients who were well until definite events or definite experiences took place. Of the five patients who were discharged with a possibly positive result of the narcoanalysis itself, four had been nervous from childhood, and an actual trauma was found in only one of the four.

If we consider the five cases in which, according to the case records,

improvement of the state set in after the narcoanalysis, which, as mentioned above, is not identical with 'because of' the narcoanalysis, the only thing that is certain is that improvement set in.

Case 1 (Case record 213/53) was a 34-year old married woman, who has been nervous from childhood and who has had many difficulties to cope with in life, thus a previous very unhappy marriage. The present marriage is not particularly harmonious, either, as the partners are very different in temperament and attitude. The provoking factor was that an 11-year old son of the first marriage had disappeared from the home a month before her admission to the department, and after that her state deteriorated seriously. This patient reacted as it were classically during the narcoanalysis, becoming very voluble, offering new information of pathogenetic interest and importance, and abreacting under great outbursts of feeling, and feeling great relief afterwards.

The actual stabilization, however, only set in after some thorough conversations with the two partners, apart and together. The boy's flight was only a provoking factor, which, however, was very significant for her, as she had a feeling of guilt towards both the boy and her husband, between whom there was the usual stepson conflict.

Case 2. (Case record 618/51). A 29-year old married woman who has always been nervous and who has had an extraordinarily straining childhood. There were some matrimonial difficulties, but no actual single experiences of any relevant psychogenetic importance. This patient also offered new information about her childhood, abreacted during the narcoanalysis and felt better afterwards; but here, too, the stable improvement only appeared after conversations with the married couple.

Case 3. (Case record 1196/52). A 38-year old married woman who also had been nervous from her childhood, which was extremely straining. She had lived in an unhappy marriage, but is now happily married. She had difficulties about a son of her first marriage, but there was no actual psychical trauma in the form of a single event which might be held responsible for the fact that she one day had an attack of hysterical aphonia. Without any outburst of feeling she offered new information about conditions in her home as a child; but the aphonia only disappeared after the last narcoanalysis and after she had thoroughly discussed her problems. She had previously suffered from aphonia which had disappeared spontaneously. She was stabilized on being discharged.

Case 4. (Case record 1320/52). A 16-year old girl who had lived in good circumstances, but who had always been nervous. Without any demonstrable cause she came to suffer from severe cancerophobia.—During the narcoanalysis she told dispassionately about her childhood, how she had always been reminded of the fact that she looked so pale and lean and that she always felt as a Cinderella. Intense aggressiveness towards her mother was also revealed. There were several conversations with her after the narcoanalysis, and she was rid of her cancerophobia.

Case 5. (Case record 618/51). A 45-year old married man, who had not been nervous before he was sent to a concentration camp. He told dispassionately about his experiences there, but did not offer new information. Some conversations were held with him after the narcoanalysis and he was stabilized on being discharged.

Indeed, it is impossible to decide whether the narcoanalysis in these cases had any decisive influence upon the ensuing improvement of the patients' conditions.

At best the patients perhaps felt it easier to unbosom themselves before the physician; but as mentioned above, this might have happened all the same and perhaps just as easily before another more easily contact-making physician. Indeed, in psychotherapy there are so many factors the importance and effect of which should not be overlooked. At any rate no immediate effect of the narcoanalysis was observed.

As a matter of fact, only in one of the five cases there was a presumably actual psychical trauma, and this is the reason why we did not experience any proper abreaction as seen in the cases from war psychiatry.

In the whole material there were only eight cases with actual relevant traumata. In this way such a hospital material of course differs highly from war time materials, and this explains the great difference between the two kinds of material as regards the therapeutic value of narcoanalysis.

The state of the 80 patients when discharged appears from the following surveys:

	Men	Women	In all
Symptomfree on discharge	2	5	7
Improved on discharge	4	13	17
Unchanged on discharge	22	34	56
In all	28	52	80

Among the 75 cases in which we dare not at all ascribe any importance to the narcoanalysis, there were 19 who were discharged in a symptomfree or improved state, and 56 who were unchanged. Among the 20 patients with narcoanalytic responses there were positive results in the five, while conditions were unchanged in 15.

All things considered, the result is not impressive, but it should constantly be kept in mind that the present material is a specially selected one consisting of patients with severe neurotic symptoms of long standing, which in more than half of the cases had existed from childhood.

An actual psychical trauma is here taken to mean a single trauma within the last two years and with indubitable release of nervous mechanisms in close connexion with it.

Of course it is very difficult to ascertain this with certainty, but I

have been so critical that, as mentioned above, I have found only eight cases, and only in one of these was the patient discharged with a good result.

We met with a single dramatic experience. The patient in question was a 34-year old woman, whose first husband committed suicide a couple of years before she was hospitalized. She was now living in a second, happy marriage, but had after her first husband's death suffered from a pronounced anxiety neurosis. Her first husband had been extremely brutal, so the marriage had been unhappy, and she did not mourn for him and did not connect her symptoms with his suicide. In the hospital she one night was dreaming that two men were pulling at each of her arms. In one of the men one half of the face was injured as if it had been shot off. This gave rise to narcoanalysis during which she in a violent outburst of passion told that she had assisted her husband in committing suicide, which was done by shooting through one temple one day when he was highly intoxicated. After the narcoanalysis she was greatly agitated, but afterwards she stuck to her explanation.

In this case there was no relief after the narcoanalysis, and the patient is not yet well after several years. Until her first marriage she was stated to be completely well and natural.

What has been stated above about narcoanalysis of course only applies to the present material, which, however, no doubt on the whole corresponds to the type of patients in other psychiatric reception departments. My experiences from private practice are in perfect agreement with my experiences from the hospital material. In my private practice I have had no cases, either, in which the effect of narcoanalysis was so striking as I have seen it in the case of hypnoanalysis.

The present results, or—if this is preferred—the want of positive results of course does not give any indications about the value of narcoanalysis as applied to quite a different material, e.g. patients with actual psychotraumatic war experiences. There the method is undoubtedly of real therapeutic importance.

As I am on principle against having criminals for psychiatric observation in my department, my experience as to narcoanalysis in such cases is poor.

A year ago, however, I had an opportunity of making an ambulant examination of a man who was charged with being an accomplice in a case of homicide. This man had repeatedly been subjected to legal-psychiatric observation, each time with practically the same result, as he was described as a pronounced inferiorly gifted psychopath, who is characterized by spinelessness, unbalanced feelings, ravings,

and a tendency towards hysteriform reactions. During the years self-assertion, unreliability, and a profound immorality and asociality seem to have become more predominant.

In the case in question there were two events about which I was to give an opinion, two events which might be of decisive importance for his case and of the evaluation of some information which the other person accused had given during hypnoanalysis. If this information could be invalidated, the other information given by the other person during hypnoanalysis must also be the object of the greatest doubt and able to invalidate the reliability of the other person accused and to weaken the confidence in the statement which the latter had made during hypnoanalysis.

About one event the man I was so examine had made a fairly detailed statement to the police; but later on he withdrew it; the other event was not mentioned in the documents of the case.

During four narcoanalyses he stuck to the statement he had made to the police. It should be pointed out that he did not himself understand that the police were at all interested in this point which was about intimate relations with the wife of the other person accused. On the other hand, he fully realized the importance of the other point, which had something to do with the alleged homosexual practices of the other person accused. Counsel for the Defence and I repeatedly pointed out to him that it was extremely important if his statement would hold good and if by a police investigation it could be substantiated that it was correct. Before the beginning of the narcoanalyses I made him repeat his information several times, and finally it was taken down in shorthand, read aloud to him, and accepted by him.

Then the other event was relived during three narcoanalyses, and each time he offered a new description of the situation, which was changed several times during the same sitting, and which was furthermore varied again after a later examination with oxygen-carbon dioxide inhalations *ad modum* Meduna, during which he was unconscious for a minute or two. He was not told what he had said during the various analyses, and some days after the last examination I asked him again to describe the situation in question. So he did, but then he showed a considerably greater uncertainty as to the decisive facts than before the narcoanalysis. On the other hand, all the indifferent incidental circumstances were remarkably alike in all descriptions.

Thus he could not as regards the central points maintain his statement, which presumably was a mixture of lies and truth, but coloured by wishful thinking and a desire for weakening the veracity of the other person accused and the importance of the hypnoanalysis. Person-

ally I believe that the former fact, concerning the wife of the other person accused, was described correctly, while the latter, which referred to the homosexual practices for economic profit of the other man accused, was a great exaggeration of what had actually happened.

I shall only add that I consider the statements made by the other person accused during hypnoanalysis to have been just as coloured and uncertain as those of the man examined by me. As in both cases we had to do with experiences which could not be verified through examination of witnesses and as to which the three principal characters, the woman and the two persons accused, each were interested in making statements which placed themselves in a favourable light, it was in the nature of things impossible to arrive at the truth about the course of events.

As far as I can see, they all lied where they thought that it would pay. During the narcoanalysis the man examined by me could not maintain his original lie, but varied it in different ways.

Unfortunately the statements of the other person accused during hypnoanalysis had not been estimated critically by the examining physician in this special case, but had only been taken down and accepted as a truthful description.

The imaginative, emotionally unbalanced, and unreliable psychopath thus did not change during narcoanalysis, as was not to be expected, either.

F. C. Redlich and his co-workers have examined the possibility of maintaining erroneous assertions during narcoanalysis. Out of nine experimental subjects only three could repeat a rehearsed false statement; the other six could not do so, but varied their statements in different ways, also so as to place themselves in an unfavourable light.

John M. Macdonald has arrived at a result similar to that of *Redlich* and states: "Criminal suspects, while under the influence of barbiturate drugs, may deliberately withhold information, persist in giving untruthful answers, or falsely confess to crimes they have not committed. Narcoanalysis is of doubtful value when used for the purpose of obtaining confessions to crimes. For ethical reasons the psychiatrist is advised against performing narcoanalysis when the examination is requested as an aid to criminal investigation."

From my own experiences and from my knowledge of the literature I have arrived at the conviction that what has been stated here about narcoanalysis on the whole also applies to hypnoanalysis, although the possibility of a suggestive influence upon those hypnotized and of giving a free rein to one's imagination in my opinion is greater than in the case of narcoanalysis.

SUMMARY

The author makes a short historical survey of the presuppositions of narcoanalysis, starting from *Benjamin Paul Blood's* self-experiments with nitrous oxide. An account is given of the result of narcoanalysis of 80 patients in a psychiatric reception department. On the whole narcoanalysis proved to be without any diagnostic or therapeutic value there.

Finally the value of the information which is obtained during narcoanalysis is discussed, especially as viewed from a criminological standpoint. The author mentions a single case which throws light on his view of this problem.

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SUBOCCIPITAL GAS MYELOGRAPHY IN THE DIAGNOSIS OF HERNIATED DISC IN THE CERVICAL SEGMENT

By

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Suboccipital gas myelography combined with tomography visualizes the spinal subarachnoid space from the occipital foramen to the terminal cistern. Gas is less irritating than positive opaque media of the abrodil (skiodan) type which are, moreover, only applicable in the lumbar region. Gas also has the advantage of being completely absorbed unlike iodized oils. Pantopaque, for instance, has been seen in the spine several years after myelography. Despite all efforts, its complete aspiration after the examination seems to be impossible.

On the other hand, gas does not, like the positive media, permit a study of the root sheaths of the spinal nerves: furthermore tomography — which is indispensable for a definite evaluation — is difficult or quite impracticable in the presence of scoliosis. The procedure also requires a tomograph with a couch that can be tilted head down. Lastly, the risk involved by any suboccipital puncture naturally restricts the indications compared with those for lumbar myelography. In addition, old persons and cardiac patients cannot tolerate the prolonged, uncomfortable head-down position.

Summing up, it may be said that the lumbar subarachnoid space is examined with opaque media of the abrodil type, the lower thoracic segment and the lumbar space with high lumbar gas myelography combined with tomography, and lastly the cervical space and the upper thoracic segment with suboccipital gas myelography. Pantopaque should be used only for old persons and cardiac patients or where abnormal curvatures of the spine prevent tomography: also in the — gradually few — cases where gas myelography fails to give a definite result.

The technique has been described by Lindgren (1939). The application of this procedure for diagnosing spinal tumours was discussed in

detail by Odén at the second Symposium Neuroradiologicum in Stockholm 1952 and case reports were submitted by the present writer in the Danish Radiological Association in 1954.

This procedure—used with negligible modifications in Lindgren's technique in the Radiological Department of the Bispebjerg Hospital

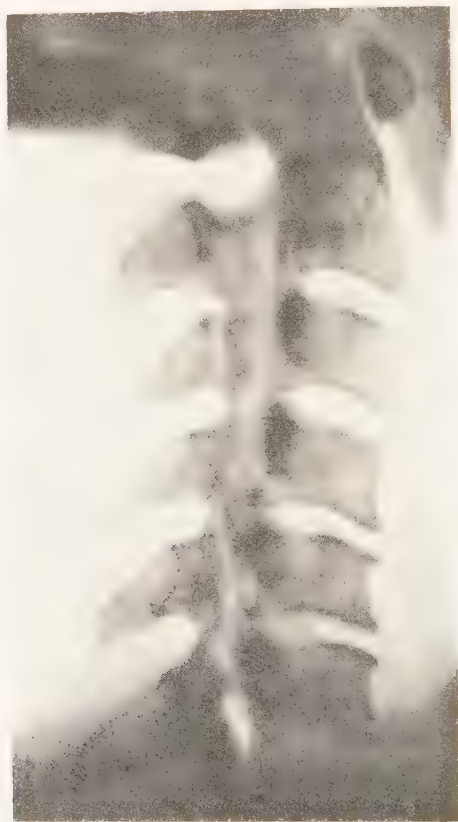


Fig. 1.

Case 2. Herniation between the 4. and 5. cervical vertebrae pressing upon the cord.

for nearly two years—is also applicable for diagnosing herniated discs in the cervical segment. In some instances there has been some diagnostic uncertainty and in others diagnostic errors have been made; the procedure requires technical routine as well as training in reading the films.

In the three cases to be reported below the diagnosis was made by X-ray and confirmed by surgery. In all three cases the histories were adequate and will not be mentioned further.

Case 1. Male, aged 56. Suboccipital gas myelography on Jan. 13, 1954 (1282/54) showed moderate protrusion of the disc between the 5th and 6th cervical vertebrae. On a level with the disc between the 6th and 7th there was a larger prominence of soft tissues into the gas shadow, very probably representing a herniation.

Operation in the University Hospital, Department of Neurosurgery on Apr. 22, 1954: "Slight protrusion of the disc between 5 and 6 without compression of the root. The disc between 6 and 7 is hard and more prominent and there is pronounced constriction of the root sheath of the 7th cervical root ...".

Case 2. Male, aged 33. Suboccipital gas myelography on March 3, 1954 (G 434/54) showed marked herniation of the thin disc between the 4th and 5th cervical vertebrae (Fig. 1). It seemed to be pressing upon the cord.

Operation on March 8, 1954 (Bispebjerg Hospital, Department of Neurosurgery): "Left-sided hemilaminectomy on the 4th cervical vertebra and the upper part of the 5th. The 5th cervical root shows some posterior prominence, and with a dissector it is possible to feel a protrusion which, however, appears to be considerably larger on the right side. Then complete laminectomy on the 4th and 5th cervical vertebrae. As expected, the protrusion is considerably larger on the right ... dura opened in the midline. The cord is displaced far backward by the protrusion ...".

Case 3. Male, aged 59. Suboccipital gas myelography on Aug. 2, 1954 (G 1391/54) showed flat protrusion of the disc between the 2nd and 3rd cervical vertebrae and a more typical herniation between the 3rd and 4th. There seemed to be a herniation also between the 4th and 5th cervical vertebrae, but at this site the appearances were more indefinite.

Operation on Aug. 4, 1954 (Bispebjerg Hospital, Department of Neurosurgery): "... extradural examination reveals a firm protrusion on a level with the disc between the 3rd and 4th cervical vertebrae. The dura was divided in the midline. At the site of the protrusion the cord looks somewhat thin and atrophic. After cutting the attachment of the ligamentum denticulatum it is possible to mobilize the dura to the extent of revealing a mass, the size of half the kernel of a hazel nut, bulging through the anterior aspect of the dura, approximately in the midline. An incision is made into the dura anteriorly and into the prominence which, as expected, proves to be an old herniation of the intervertebral disc".

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SCLÉROSE EN PLAQUES

ÉTUDE PATHOGÉNIQUE ET SOCIOLOGIQUE

Par

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Au cours des dernières années, nous avons attiré, dans plusieurs conférences et articles, l'attention sur l'importance sociale de la sclérose en plaques. D'après nos connaissances actuelles, la sclérose en plaques a déjà évolué au-delà de l'intérêt manifesté par le neuropathologiste, et elle constitue de nos jours un problème social d'une telle ampleur qu'il approche celui de la tuberculose et de la syphilis.

Cette conception se fonde sur les faits suivants: 1° l'étiologie de la maladie est inconnue; 2° après la neurosyphilis, c'est la maladie nerveuse la plus fréquente; 3° la durée de la maladie peut être fort longue; 4° aucun médicament efficace contre cette maladie n'a été découvert; 5° après une durée plus ou moins longue, elle détermine toujours l'incapacité du travail.

I. — LE PROBLÈME DE L'ÉTIOLOGIE

On distingue cinq groupes étiologiques dont voici le tableau, en abrégé:

a) La *théorie de l'infection virale*. Ses disciples sont: en France, *Guillain* et son école; au Danemark, *Knud H. Krabbe*; en Allemagne, *Jakob, Schaltenbrand, Hallervorden*; en Grande-Bretagne, *Bullock, Wilson, McAlpine* et *Compston*; en Union Soviétique, *Margoulis, Soloviev* et *Shoubladzé*.

b) La *théorie hétérotoxique*, fondée par *Campbell* et coll. sur leurs propres observations concernant la teneur en cuivre du sol ou la teneur saturnine du sol et de l'eau potable.

c) La *théorie autotoxique* prend son point de départ dans la myélinolyse de *Marburg* (1909), hypothèse que *Brickner* a essayé de démontrer, en 1930, dans des expériences sur les rats. A partir de 1930, toute une lignée de chercheurs ont pris parti pour la lipolyse. Selon *Lafontaine*, toutes les humeurs tissulaires (sérum, plasma, liquide cé-

phalo-rachidien, urine) des malades atteints de sclérose en plaques contiennent des matières myélinolytiques. D'autres chercheurs ont cru trouver la cause de la maladie dans des désordres biochimiques et enzymatiques (*Lumsden*), dans l'effet endotoxique (*Weil, Baker*) ou dans le métabolisme carbohydraté anormal (*Huszák*).

d) La *théorie allergique*, créée en 1927 par *Glanzmann* et soutenue par *vanBogaert, Pette* et *Ferraro*, n'a été réellement étayée que ces dernières années, par les essais sur les singes (*Schwentker* et *Ferraro*, *Ferraro* et *Jervis*, etc.). Ils ont réussi à obtenir, non seulement avec la substance hétérologue, mais également avec la substance homologue, un effet anti-cerveau qui est plus fort dans la substance blanche que dans la grise. Ces altérations histologiques sont conformes aux caractéristiques histopathologiques de l'inflammation allergique. Récemment, on a également réussi à provoquer, sur le cobaye (*Alvord* et *Stevenson*), le Chien (*Halpern, Bertrand* et *Lhermitte*) et le lapin (*Waksman* et *Morrison*) de l'encéphalomyélite allergique ou isoallergique, la démyélinisation.

La plupart des cliniciens ont accueilli favorablement la conception allergique parce qu'elle leur permettait d'expliquer l'exacerbation subite dans la sclérose en plaques, son amélioration également prompte et la fugacité des symptômes. Plus attrayante encore est l'hypothèse auto-allergique de *Gozzano*, que *Voisin* (1954) a élargie en syndrome de la « maladie auto-entretendue ».

e) Enfin, la *théorie vasculaire* prend son départ de la présence de thromboses multiples, *primaires* d'après *Putnam* et son école, mais *secondaires* selon leurs contrôleurs (*Dow* et *Berglund*; *Scheinker, Broman*), c'est-à-dire une séquelle de foyers démyélinisés.

Zimmermann et *Nelsky*, ainsi que *Adams* et *Kubik* n'ont trouvé de thrombose ni dans les plaques ni aux bords de ces dernières.

Dans cette question discutée, les données résultant de nos propres recherches histologiques sont les suivantes: Dans 20 cas de sclérose en plaques, nous avons observé un caillot sanguin au niveau des capillaires ou des artérioles, 1 fois dans le foyer développé et 14 fois dans les alentours du foyer ou dans le tissu nerveux « intact », distant du foyer.

Nous fondant sur les données littéraires et les nôtres, nous devons conclure que l'origine thrombotique des foyers de la sclérose en plaques n'est pas vérifiée, cependant on rencontre des caillots et leur présence est un fait qui, dans l'étiologie, doit être considéré sous l'aspect de l'allergie (voir plus loin).

La révision des divers domaines de recherche nous permet de distinguer trois phases de la maladie: 1° *initiale*, 2° *de latence* et 3° *de l'évolution complète ou de démyélinisation*.

1° Dans la *phase initiale*, le sujet s'adresse, non à un neurologue, mais à un *oculiste*. L'explication en est que, dans les antécédents de la sclérose en plaques, la fréquence de la névrite rétrobulbaire est, selon la plupart des auteurs (Marburg, Windmüller, Yaskin et coll., R. Müller, etc.) au-dessus de 50 %, de 70 % d'après Curschmann, Kampherstein, et même de 75.4 % suivant Behr. Vraisemblablement il se forme, dans ces cas, au niveau du nerf optique, de petits foyers inflammatoires et oedématisés qui tendent à involuer et qui disparaissent en quelques jours ou en quelques semaines. Mais ces foyers se rencontrent non seulement dans le nerf optique, mais également dans le trajet postérieur du système optique, c'est-à-dire dans le chiasma, le corps genouillé latéral et dans les radiations optiques.

Nous devons ces acquisitions anatomo-pathologiques aux observations d'Oppenheim, d'Uthoff, de Völsch, etc. Les cas autopsiés qui présentent un intérêt particulier sont ceux d'Oppenheim et d'Uthoff, où, malgré les foyers optiques, la constatation ophtalmoscopique chez les sujets était entièrement normale de leur vivant.

Nos propres données embrassant vingt cas révèlent des foyers de sclérose en plaques ou des altérations histologiques correspondant à des foyers, au niveau de la substance blanche voisine de la corne postérieure, pour 85 %, au niveau du chiasma et de la substance blanche entourant la corne inférieure, pour 45 % et 50 % respectivement, dans la bandelette et le nerf optique, pour 45 %, et dans le corps genouillé, pour 25 % des cas.

Sur la base des données cliniques et pathologiques mentionnées, la lésion du système optique périphérique ou central en tant que siège peut être considérée comme lieu de préférence de cette affection, ce qui ferait supposer que l'agent inconnu envahit le système nerveux par la voie du nerf optique.

Comment l'agent pathogène pénètre-t-il dans le nerf optique? Il est possible que le contagion arrive par l'intermédiaire d'une infection par gouttelettes sur la cornée et la conjonctive oculaire d'où il sera charrié sur les limbes et parviendra à l'aide de la communication veineuse dans la veine ophtalmique. (Nos essais sur les animaux en vue d'éclaircir ce problème sont en cours).

On n'ignore pas qu'une partie des maladies virales connues est transmissible par la conjonctive et la cornée. Telles sont, par exemple, la rage, la poliomyélite, l'encéphalite léthargique, l'encéphalite herpétique, etc. Dans une partie de ces cas, il a été possible de mettre en évidence que la conjonctive permet une contamination spontanée (Lépine et Sautter).

Notre hypothèse est donc que, dans le stade primitif de la maladie, une matière inconnue, un contagion, pouvant être un virus, entre dans

l'œil et de là, dans le système optique périphérique et central. Les données de *Störtebecker* et de *Fog* (la vitesse de sédimentation accrue des globules rouges et le nombre leucocytaire augmenté, ainsi que l'agglutination élevée des plaques sanguines) font plutôt conclure à une infection.

Que se passe-t-il ultérieurement dans le système nerveux central?

Les données de *McAlpine* et de *Margoulis* permettent de supposer que l'agent pathogène inconnu est principalement diffusé par la dissémination hémotogène et, dans une moindre partie, par les nerfs périphériques. Ici, nous rappelons les données de *Sachs*, *Steiner* et de leurs contrôleurs, ainsi que celles de *Lafontaine*. *Margoulis* a pu démontrer, dans le sérum, chez 50 % des malades, un anticorps capable de neutraliser le virus.

Nous étions donc amenés à penser que les petits foyers inflammatoires primaires du système optique, en voie de décomposition, déclenchent dans le tissu nerveux de ce dernier une production d'anticorps. *Cet anticorps ou antigène parvient, au moyen de l'essaimage hémotogène, partout dans l'organisme et dans toutes les parties du système nerveux central.* Cette circonstance expliquerait le fait que, dans le III^e stade de la maladie, les foyers démyélinisés ne sont pas liés au système optique, mais se retrouvent à n'importe quel endroit du cerveau et de la moelle épinière et même dans les nerfs encéphaliques ou périphériques.

D'abondantes données bibliographiques (*Oloff* et autres) concernant le II^e stade, la latence, nous apprennent que cette période peut durer 8, 36 ou même 46 ans. *Nos propres données* fixent ce temps de 2-3 à 12-15 ans. Dans la pathologie du système nerveux central, cette longue incubation n'est pas inconnue: la période de latence de l'encéphalite épidémique, durant plusieurs années, parfois plus d'une dizaine d'années, en est un exemple.

Nous tenons pour possible que, pendant l'incubation de la sclérose en plaques, le système nerveux se trouve dans un état hyperergique.

Dans le stade suivant, le III^e stade ou période de démyélinisation, le malade va consulter le neurologue. Ceci est concevable, étant donné qu'en ce moment les foyers disséminés sur le territoire du système nerveux entier, donc dans la moelle épinière aussi, produisent des symptômes nerveux multiples.

On dispose, dans ce stade, de maintes données qui étayent le rôle de l'allergie, telles que:

a) En clinique, la production rapide des symptômes et leur caractère fugace, qui se prête difficilement à une autre explication qu'à celle des oedèmes locaux (*Foster Kennedy*). L'épaississement de la

paroi de la veine rétinienne et la périphlébite observés par *Rucker* doivent être considérés comme des lésions vasculaires primaires, étant donné que les fibres nerveuses de la rétine ne disposent pas de gaine myélique. Son observation a été vérifiée par *Silferkiöld*. Selon cet auteur, la sclérose en plaques est également susceptible de se manifester sous forme de périvascularite des vaisseaux rétiniens. *Haarr* est pour l'origine allergique de la périphlébite.

b) Les *données histologiques* n'intéressent notre problème que pour les *critériums de l'inflammation allergique*. En grandes lignes, ce sont les suivants:

- 1° altération du système vasculaire;
- 2° oedèmes périfocal et périvasculaire;
- 3° production de *granulomes*;
- 4° lésions périvasculaires du parenchyme.

En ce qui concerne ces points, nous ferons connaître ci-dessous les conclusions finales de l'examen histologique très détaillé de nos vingt cas de sclérose en plaques:

1° Dans la plupart de nos cas, nous avons constaté les conditions suivantes: préstase, stase, dilatation capillaire et des petites vaisseaux, thrombose, dégénérescence hyaline de la paroi vasculaire, oedème capillaire, et, dans un tiers des cas, de petites hémorragies.

Dans la neuro-allergie, l'importance de ces altérations est soulignée par *Ferraro*. D'après lui, la similitude s'étend à tous les facteurs et les différences s'expliquent par le fait que la sclérose en plaques est un processus se prolongeant pendant des années et que de cette façon, il faut prendre en considération le facteur *temps* dans l'appréciation du tableau histologique. Selon *Gomirato*, toutes les altérations vasculaires de l'inflammation allergique se retrouvent dans la sclérose en plaques.

Dans 19 cas sur 20, nous avons trouvé une altération vasculaire inflammatoire (infiltration périvasculaire), se produisant chez 8 malades, dans le voisinage du foyer, mais parfois aussi à une plus grande distance de ce dernier. Sur cette base, nous sommes amenés à qualifier l'inflammation rencontrée dans la sclérose en plaques comme appartenant au *véritable type, forme primaire, donc non symptomatique*.

2° *L'oedème périfocal*, c'est-à-dire la « spongiosité » périfocale, se rencontrait dans 19 cas sur 20 et l'oedème tissulaire distant du foyer (« *Mottenfrass* », « *trou de mites* »), dans 17 cas.

Dans la sclérose en plaques, ces deux formes de l'oedème tissulaire ont été décrites par *Borst* en 1897 et 1904, c'est-à-dire bien avant

l'avènement de l'ère allergique. Plus tard ce n'étaient que Anton et Wohlwill, puis *Siemerling* et *Raecke* qui ont fait état d'altérations analogues.

3° *Dans 60 % de nos propres cas, nous avons trouvé des micro-granulomes capillaires ou périvasculaires*, bien que ce fussent des cas invétérés, remontant même à une dizaine d'années. Il est connu que la formation de *granulomes* est, d'après les essais de *Campbell* et *Goddard*, un facteur très important dans le tableau histologique neuro-allergique de la substance nerveuse.

4° *Dans tous nos cas, nous avons rencontré des lésions parenchymateuses périvasculaires, parfois même dans la substance blanche distante du foyer et nous les considérons, pareillement à Borst, ainsi qu'à Adams et Kubik, comme des microfoyers.*

Compte tenu de ce qui précède, nous résumons notre manière de voir dans ce qui suit:

L'histopathologie de la sclérose en plaques révèle maintes données plaidant en faveur de la « réaction hyperergique ». Séparément, chacun de ces signes peut se rencontrer dans tout processus morbide. *L'ensemble* et la tendance à se grouper de ces altérations pathologiques nous paraissent cependant autoriser à attribuer à la réaction allergique un rôle très important dans le troisième stade, celui de la démyélinisation.

Outre les constatations histopathologiques, nous énumérerons les données suivantes:

1° Dans la sclérose en plaques, *l'harmonie des données cliniques et pathologiques exigée par Aschoff se trouve réalisée.*

2° Parmi les *examens expérimentaux*, la démyélinisation obtenue à l'aide des tissus cérébraux homologue ou hétérologue.

3° Les données des *examens bio et immuno-chimiques*: la *perméabilité capillaire* des malades atteints de sclérose en plaques est beaucoup plus élevée (*Huszák*) et cette augmentation est en proportion de la gravité de la maladie (*Könyves, Kolonics et Huszák*). Parmi les *données sérologiques* nous rappelons les suivantes: l'indice d'adhérence des plaques de sang est anormalement accru selon *Nathanson* et *Savitzky*, à savoir: dans la phase active de la sclérose en plaques, pour 82 % et dans l'exacerbation aiguë, pour 100 %. *Sachs et Steiner* ont réussi à mettre en évidence des anticorps dans le sérum des malades atteints par la sclérose en plaques, fait confirmé par *Frick*, ensuite par *Schrader* et *Schild*, puis par *Schild, Schrader et Römer*.

4° *L'action de l'extérieur ou effet du terrain* détermine, en quelques heures ou quelques jours, des foyers récents: leur fréquence est de 32,6 %.

5° D'après les observations de *McAlpine et Compston* sur leur population hospitalière atteinte de sclérose en plaques, la fréquence des dérèglements allergiques se monte à 27 % contre 16,8 % de sujets indemmes de la maladie.

En résumé, on pourrait dire que les données cliniques, expérimentales, histopathologiques et biochimiques, ainsi que l'harmonie clinique et pathologique et aussi certaines observations, confirmant l'effet du terrain, plaident, dans le III^e stade, celui de la démyélinisation, pour la grande probabilité du mécanisme allergique.

Conformément aux faits exposés, nous soulignons que, selon toute vraisemblance, plusieurs facteurs figurent dans l'explication pathogénique de la sclérose en plaques, mais *il est probable que, dans les divers stades de la maladie, c'est toujours un autre facteur qui agit.*

Il est possible que dans le 1^{er} stade, c'est-à-dire la période initiale, c'est un agent pathogène, tel un virus, et dans les II^e et III^e stades, c'est un facteur allergique qui préside.

II. — LA FRÉQUENCE DE LA SCLÉROSE EN PLAQUES

Sous ce rapport, la sclérose en plaques vient immédiatement après la neurosyphilis. Dans les grands établissements neurologiques étrangers, sa fréquence est de 3,9-8,7 % (*Alpers, Brain, Wilson*) ; à la section neurologique de l'Hôpital István de Budapest, elle est de 6,8 % en dix années.

La *morbidity générale* dans différents pays oscille entre 0,04 ‰ (États-Unis: *Trager, Wilson*) et 0,7-0,8 ‰ (Danemark: *Knud Winther*). En Hongrie, les données concernant la morbidité sont les suivantes: la population civile appartenant aux cinq centres de consultation neurologique compris dans la circonscription hospitalière de l'Hôpital István, s'élève à 635.000 personnes dont 106 étaient frappées, en 1952, de sclérose en plaques, chiffre équivalant à 0,016 ‰. En outre, aux mois de mars et d'avril 1953, dans la population de 600.000 habitants du rayon sud de Budapest, il y avait, selon les rapports des médecins de districts, 131 cas de sclérose en plaques, correspondant à 0,021 ‰. En nous basant sur ces grands chiffres, nous *estimons la morbidité générale à 0,02-0,05 ‰.*

III. — LONGUE DURÉE DE LA MALADIE

Le cours de la sclérose en plaques s'étendant sur plusieurs dizaines d'années est aujourd'hui généralement connu. La durée moyenne de la vie s'élève, d'après *Mackay*, à vingt ans, mais 6,5 % de ses malades

ont vécu plus de 20 ans (23 à 49 ans). Parmi les données de *Carler* et coll., cette durée est de treize ans, la plus longue de 64 ans. La durée de la rémission chez deux malades de *H. D. McIntyre* et *A. P. McIntyre* était de 18 ans, chez un autre de leurs sujets de 20 ans. Un patient de *McAlpine* et *Compston* était en rémission pendant 37 ans. Parmi les 100 sujets de *Thygesen*, le quart des malades était encore à même de travailler après 8 à 15 ans de maladie.

Parmi nos 100 sujets atteints de sclérose en plaques, *nous avons pu observer chez 5 patients, dont 4 femmes et 1 homme, une durée de maladie de 16, 20, 20, 24 et 27 ans respectivement, de façon que ces malades ont pu vaquer très longtemps à leurs occupations (13, 15, 16, 20 et 22 ans respectivement)*. La répartition selon l'état est, chez les femmes: 3 sans profession, 1 ouvrière de fabrique; l'homme était un serrurier ayant du travailler encore pendant treize ans dans son métier. Chez quatre autres femmes, la maladie a duré 13 ou 14 ans et les malades ont gardé leur capacité au travail pendant 6, 8 ou 10 ans à partir du début de l'affection. Un homme de 50 ans mérite d'être spécialement mentionné: sa maladie a débuté il y a 14 ans par une diplopie, et bien que le malade ait dû changer de profession (auparavant chauffeur, maintenant il est serrurier), il est capable d'exercer son métier.

Certes, ces exemples sont des exceptions. La plupart des cas sont constitués par des sujets qui deviennent invalides en quelques années. D'après l'excellente statistique de *Ragnar Müller*, 40 % des malades deviennent invalides en cinq ans et 80 %, au bout de dix ans. Selon *Kolb*, après cinq ans, 80 % des sujets sont inaptes au travail et 75 % contraints à l'abandonner au cours de la première année. Les données de *McLean* et *Berkson* sont plus favorables: les 64 % des malades ont été à même de travailler après cinq ans, et 42 % après dix ans.

L'exacerbation progressive est due, en général, à ce que, selon *Thygesen*, les malades sont frappés, tous les dix mois en moyenne, d'une nouvelle « poussée » produisant de nouveaux symptômes. Dans la sclérose en plaques, *Swank* a trouvé morbide dans un haut pourcentage le chromatogramme des protéides du plasma, exécuté dans des cycles de 1 à 3 mois.

IV. — LE PROBLÈME DU TRAITEMENT DE LA SCLÉROSE EN PLAQUES

Étant donné que l'on est réduit à des essais thérapeutiques ou au traitement symptomatique (voir les publications de *Lehoczky* et de *Schumacher*), la tâche médicale la plus importante est d'élaborer pour

les malades un *plan de réhabilitation*. Pour cela, il faut connaître de manière précise l'extension et le degré de la paralysie et de l'incoordination, la fatigabilité individuelle du sujet et sa volonté à guérir. Celle-ci doit être soutenue fermement, avec un optimisme inébranlable, étant donné que l'attitude indifférente ou négative du médecin peuvent avoir des conséquences très fâcheuses pour le malade. « Tant que l'on ignore ce que l'on peut espérer de la réhabilitation, il vaut mieux adopter le point de vue optimiste que pessimiste » - dit très justement *Alexandre Adler*.

Nous ne rappelons que furtivement *les problèmes de la réhabilitation*.

Les symptômes tels que la parésie, l'ataxie, la spasticité, l'automatisme spinal, la paresthésie, la douleur et les troubles de la vision doivent être appréciés séparément et individuellement.

La méthode princeps de reconditionnement, le rétablissement fonctionnel du muscle parétique ou plégique, est l'exercice musculaire, actif et persévérant, dont une des formes est la marche subaquatique préconisée par Lowman, ainsi que d'autres exercices. Les exercices passifs se prêtent moins à la rééducation, étant donné que *le muscle doit être activé par lui-même*. La contracture ne doit pas être traitée mais prévenue, d'où la nécessité de veiller avec attention, dès le début, au mouvement des extrémités, à la position assise du malade, etc. Aussi faut-il chercher à amplifier *individuellement* les exercices connus de correction de *l'ataxie*, ou mieux de l'incoordination.

La *spasticité* est réduite à l'aide de massage, de chaleur, d'exercices de relâchement, d'infiltration locale à l'acétylcholine du muscle. Le curare, la myanésine, le tolsérol sont d'un effet fugace qui souvent peut même faire défaut.

En cas d'*automatisme spinal*, certains auteurs recommandent la rhizotomie antérieure entre D 11 et S 1, Gordon cependant ne l'indique qu'au cas où la parésie spastique est devenue atonique. Sommer est pour l'infiltration procainique des ganglions symétriques L. 1 et L. 2 ou bien pour l'injection intrathécale de 15 cc d'alcool. La *paresthésie* se rencontre dans 44 % et elle est généralement le symptôme le plus difficile à influencer. Son importance réside en ce qu'elle évoque constamment, chez le sujet, le fait d'être malade et qu'elle diminue la capacité au travail. - La fréquence des *troubles de la vision* (n. II + III) s'élève à 83 % : ce symptôme atteint souvent un degré qui ne permet au malade ni d'écrire ni de lire. - On a observé dans 42 % des douleurs (*Carter, Sciarra et Merritt*) : pour les supprimer, on utilise les méthodes habituelles dans la radiculonévrite. Les *troubles de la*

miction et des évacuations alvines se rencontrent principalement dans le stade de la paraplégie complète. Rarement, elles peuvent constituer un signe précoce, et même le *premier symptôme*, comme nous venons de l'observer récemment dans trois cas. L'objectif du traitement est, dans ces cas, d'obtenir une vessie dite de réflexe.

V. — LA SCLÉROSE EN PLAQUES ET L'APTITUDE AU TRAVAIL

Pour pouvoir apprécier la capacité au travail des malades atteints de sclérose en plaques, nous avons totalisé les données de *cent sujets au moment* où ils ont quitté notre Section :

Aptitude parfaite au travail	32
„ diminuée „ „	18
Inaptitude au travail	50
	100 cas

Par conséquent, *grosso modo* un tiers de nos malades est apte au travail, un cinquième est physiquement diminué et la moitié devient totalement incapable au travail.

Dans la colonne des capables de travailler, on trouve les cas de sclérose en plaques suivants : peu graves, 16 ; moyens, 14 et sévères, 2. Parmi les cas graves, citons une femme de 63 ans, malade depuis dix ans, qui accomplit son travail de ménagère malgré sa paraparésie sévère, et un pasteur de l'église réformée, âgé de 35 ans, qui se trouve dans un état ataxique, paraparétique grave depuis onze ans : il remplit sa vocation.

Dans le groupe des physiquement diminués, on trouve la répartition suivante : cas peu graves, 7 ; moyens, 8 et sévères, 3. Six de ces malades ont dû choisir, au lieu de leur ancien travail, stationnaire ou ambulatoire, une autre profession, sédentaire. Neuf de nos sujets vquaient, jusqu'au début de leur maladie, à leurs occupations ménagères, ce qu'elles continuent à faire. Trois des malades (un mécanicien de précision et deux employés de bureau) n'ont pas voulu changer de profession (le premier appartient au groupe des cas graves, les deux autres à celui des cas moyens).

Nos données concernant les *infirmes* sont très importantes : 39 malades sont incapables de travailler depuis 1 à 5 ans et 11 malades depuis 6 à 24 ans. L'incapacité au travail s'est établie, après une durée de maladie allant de six mois à trois ans, pour 15 cas ; de 4 à 10 ans, pour 30 cas et de 14, 15, 16, 20 ou 22 ans, pour 5 cas. *Il en ressort que la*

scélérose en plaques déclenche, dans la majorité des cas (60 % dans ce groupe), l'inaptitude au travail après une durée de quatre ans.

Nous avons observé moins fréquemment que le malade devient infirme au cours de la première année ou au début de la maladie. Nous l'avons constaté chez 5 sujets dans le premier cas et chez 4 dans le second (5 % et 4 % respectivement).

Lorsque les malades frappés par la scélérose en plaques sont envoyés au travail, il faut tenir compte de leur susceptibilité accrue d'être accidentés (accident prontness) d'origine somatique ou psychique (*Bennet*). Par suite de ses symptômes organiques, le malade peut facilement se trouver dans une situation dangereuse soit dans la rue, soit à son lieu de travail. Parmi les symptômes psychiques, l'euphorie des sujets et leur sens critique diminué contribuent à augmenter cette disposition à subir des accidents. Ce changement, euphorique et sans critique, de l'équilibre moral a pu être observé dans 51 % de notre population hospitalière en question.

Il convient de souligner que les soins hospitaliers et les consultations externes sont incapables de résoudre seuls le problème de la réhabilitation de la scélérose en plaques.

A notre avis, la restitution de la capacité au travail des malades atteints de scélérose en plaques ne peut être atteint qu'au moyen d'établissements analogues aux sanatoriums antituberculeux. Ce fait est d'autant plus important, parce que -- comme nous l'apprennent les données de *R. Müller* -- c'est la première année qui décide de l'allure et du pronostic de la scélérose en plaques. Si le sujet s'est ménagé pendant ce temps, les perspectives d'une rémission complète sont infiniment meilleures. Le repos de longue durée est, selon *Freeman*, aussi le plus important.

Ce n'est que le repos prolongé (de trois ou six mois, d'un an) dans des préventoriums ou des établissements spéciaux pour convalescents qui permet de protéger le malade en rémission de la rechute et de maintenir son immunomécanisme en équilibre.

En attendant que l'étiologie soit éclairci et que la thérapeutique causale se réalise, notre tâche la plus urgente consiste à organiser avec beaucoup de soins et de circonspection l'œuvre de l'assistance sociale.

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REMARKS ON THE STURGE-KALISCHER-WEBER- DIMITRI-KRABBE DISEASE

By

HERMAN LEVISON

On going through the literature *Krabbe* is seen to have contributed much the largest collective clinical survey of the congenital vascular anomaly by *Bergstrand* called the *Sturge-Weber Disease*.

While *Schirmer* in 1860 described a telangiectasis *Sturge* in 1879 mentions the probable connection between a visible telangiectasis on the right side of the face and a supposed similar vascular anomaly on the right side of the brain with leftsided focal epileptic convulsions.

Kalischer in 1901 presented the autopsy findings in the brain of a patient with similar telangiectasic changes.

In 1922 and 1929 *Parkes Weber* presented roentgenological intracranial changes on the same side as the cutaneous telangiectasis and showed the typical double-contoured sinuous lime shadows. Similar changes were observed (but not reported) the year before (1921) by the *Dane Wissing*.

In 1934 *Krabbe* published his great work in which he mentions five cases of the disease for which he suggests the name of *Parkes Weber-Dimitri Disease*. The descriptions are typical, and the typical sinuous intracranial lime shadows are found in the x-rays. *Krabbe* further presents the result of the autopsy of the brain in which he points out that microscopically there appear small granules of lime as well as conglomerates of them, chiefly in the second and third layers of the cerebral cortex without any relation to the vessels displacing glia and neuroglia. The lime shadows to be seen in the x-rays are not vessels, but the picture of the gyri of the brain, where the rays strike parallel to the deep going calcareous parts of the cortex.

Weber in 1946 finds no reason to add his name to the disease and suggests calling it the *Sturge-Kalischer Disease*.

On the basis of the microscopy of the brain of the patient suffering from the syndrome discussed *Lichtenstein* (1954) stresses that the cerebral hemangiomatosis chiefly is localized to the leptomeninges, but that smaller angioma-formations may also occur in cortex and the sub-



Fig. 1.
Hemangiomatosis.

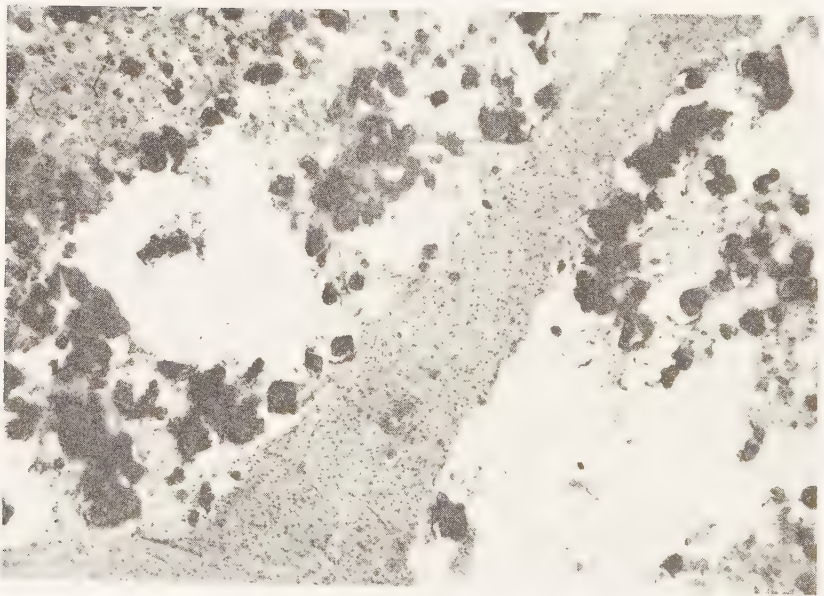


Fig. 2.
Lime granules in cortical layers.



Fig. 3.

B. S., 12 years. Nevus in the left frontal region.



Fig. 4.

B. S., 12 years. Small nevus on the right side of the nose.

cortical white substance. Cortex exhibits two pictures under the microscope: 1) a complete or next to complete absence of nerve cells with diffuse gliosis and obliterary pericapillary fibrosis. 2) Pericapillary alterations as well as round and more irregular vascular vessel formations in cortex with disturbance of the cytoarchitecture as well as gliosis. The changes are probably due to a disturbance of the metabolism of the cortical tissue owing to the venous stasis. If a pronounced disturbance occurs early the complete absence of nerve cells with reactive gliosis and slight calcification sets in. If nutrition eventually and gradually increasingly is compromised a considerable amount of lime and iron may be deposited. If the subcortical medullary substance is affected by the pronounced vascularisation glial degeneration and calcification arise. Though the nutritive degenerative alterations in cerebrum may be progressive the disease decidedly seems to be due to predisposition, presumably a mesenchymal formation originating in the neural crest.

By an examination made by me of microscopic sections from the brains of patients suffering from the cerebral and cutaneous hemangiomas discussed *Lichtenstein's* views seem to be confirmed (Figs. 1 and 2)¹. The alterations are more manifold than described by

¹ From the Neurosurgical University Clinic in Copenhagen. Head: Professor E. Busch. Neuropathologist: Erna Christensen, M.D.

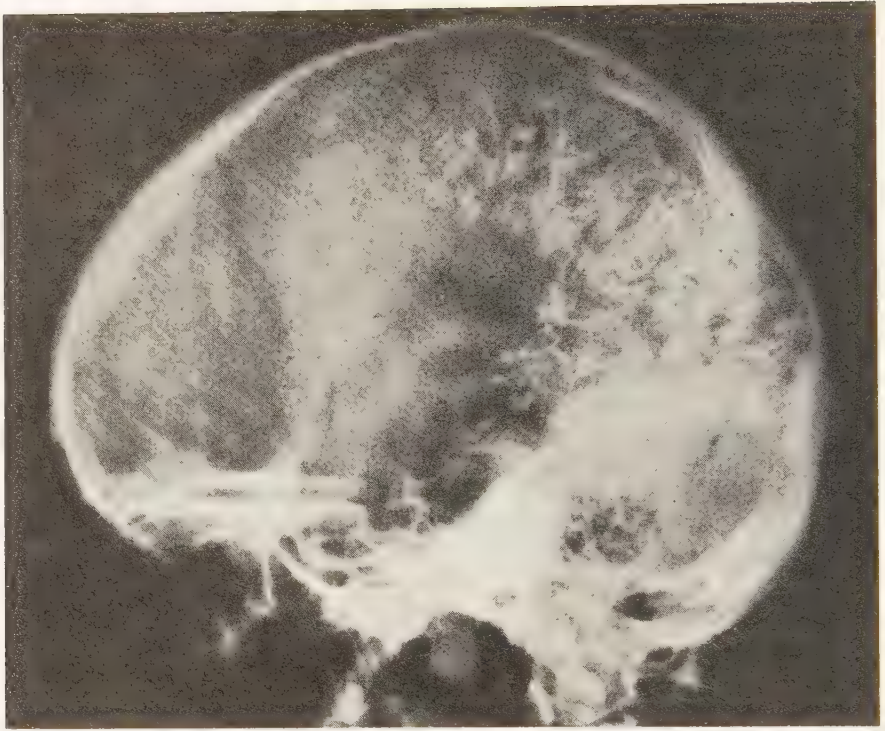


Fig. 5.

Krabbe: there occur both leptomeningeal as well as parenchymatous hemangiomatosis with complete absence of ganglial cells in cortex and severe venous vascularisation with a majority of small grained calcifications in the various layers of cortex and the white substance.

The hemangiomatosis must be stressed as the primary feature of the picture. The cerebral disturbances are focal or universal epilepsy, defective mental development as well as hemiplegia. These in connection with the characteristic roentgen findings of sinuous, double-contoured lime shadows intracerebrally form the syndrome. *Krabbe* further stresses adiposity.

Though well-known the disease seems to be rare. In 1935 *Bergstrand* had been able to find only 80 cases since 1860. *Mogens Lund* reports 144 cases gathered from the literature.

Figs. 5, 6, 7: B. J. 12 years. Radiograms of the skull. Tortuous double-contoured lime shadows in the left hind-brain.

*Fig. 7.**Fig. 6.*

A clinically typical case will be demonstrated¹:

A twelve-year old girl B. J. From birth nevus on the left side of the forehead as well as on the left side of the back of the skull. At the age of seven months stiffness was noted at the back of the neck, vomiting, and light convulsions in the right arm. The seizures increased in strength and frequency in the course of years, they are released by even slight bruises particularly on the left side of the head. The seizures may last from one hour to 48 hours.

The patient has always been mentally retarded, cannot now attend normal school.

On May 16th she was struck by a ball on the left side of the head, which released a rightsided epileptic seizure that lasted for 48-70 hours. During the seizure she contracted a temperature (38.2° centigrades), she was partly unconscious.

On admission to hospital on May 18th, 1954 under the said epileptic seizure she was found torpid with her head turned to the left and stiffness of the neck. On the left side of the frontal region and round the left eye is a large nevus with sharp limitation towards the centre line (Fig. 3). On the right side of the nose is a small slightly raised nevus of the size of a pea (Fig. 4). On the left side on the back of the skull under the hair is a small nevus.

There was rightsided facial paresis of a supranuclear (central) type. Further a pronounced rightsided hemiparesis, most marked in the arm + Babinski signs on the right side. Owing to the very poor condition of the patient no lumbar puncture was undertaken.

By a control examination on July 7th, 1954 were found: 1) Distinct mental retardation, 2) Normal state of nutrition, 3) Nevus on the skin as demonstrated, no angioma in the mouth, 4) Distinct aphasia with regard to difficult words, 5) Slight rightsided hemiparesis affecting right side of the face, the right arm and right leg, increased rightsided deep reflexes, slightly positive rightsided Babinski signs, rightsided abdominal reflexes weakened, 6) Examination of eyes: By ophtalmoscopy no sign of angioma formation, 7) On the skin some neurofibromata.

X-ray showed the typical double-contoured sinuous lime shadows in c. $\frac{1}{3}$ of the left cerebrum (Figs. 5, 6, 7). An operation was not indicated, and the patient now attends a school for lighter mentally deficient pupils.

SUMMARY

It is natural to add *Krabbe's* name to the well-known, though rare, hemangiomatous dysplasia on the skin and in cerebrum: *Sturge-Weber-Dimitri-Kalischer-Krabbe's Disease*, as *Krabbe* has provided the most extensive collective clinical description. The microscopical conditions do not seem to be as mentioned by *Krabbe*. Angiomatosis is found in the leptomeninges, and also in cortex and the medullary substance causing localized nutritive, partly progressive, changes in the various layers of the cerebral cortex as well as in the medullary substance with or without lime deposits. A typical clinical case is demonstrated.

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KERNICTERUS

A Clinical and Pathological Study of Two Late Cases

By

MOGENS LUND

Introduction.

Interest in the neurological sequelae of kernicterus has grown of late on account of the more active therapeutic attitude towards what is called cerebral palsy. Early in 1952, two children with athetosis were admitted to the Neurological Department of the Odense County and City Hospital. Both patients developed hyperthermia and a condition recalling decerebrated rigidity and died. An autopsy of the brain was performed in both cases. As there are but few pathological studies of cases of kernicterus having survived the neonatal period, publication of these two cases seems justified.

The acute phase.

Post-natal icterus of the basal ganglia was first described by *Orth* in 1875. The name "kernicterus" is ascribable to *Schmorl*, who in 1903 described the pathological findings in infants who had died of icterus gravis. Later came the description of the familial cases. After the discovery of the rhesus blood type it was recognized that the majority of familial cases were due to rhesus isoimmunization.

The pathological findings in the acute phase are well-known. In the brain they are localized particularly to the hippocampus, nucleus sub-thalamicus, putamen, globus pallidus, the caudate nucleus, the inferior olive, the dentate nucleus, the vermis and flocculus, and in the severe cases to the nuclei of the floor of the fourth ventricle.

The clinical picture is also familiar. The icterus has an early onset and is severe, the child becomes limp and it screams, it refuses to drink, and there may be opisthotonus, rigidity, cyanosis, periods of apnoea; clonic convulsions and coma precede death.

When the aetiology of icterus gravis neonatorum and kernicterus

proves to be isoimmunization the clinical picture is called erythroblastosis foetalis or haemolytic disease of the newborn, but this is not the aetiology in about half of the cases; these will preponderantly be premature babies (*Zuelzer and Mudgett 1950*). The very premature babies die. The syndrome and brain pathology are almost identical.

The pathogenesis of the encephalopathy will not be discussed here.

Frequency.

According to *Perlstein (1952)*, kernicterus owing to isoimmunization was formerly responsible for about 10 % of all cases of cerebral palsy. According to *Perlstein*, the figure is now only 3 %. He considers the cause of the decrease to be public enlightenment and also treatment with replacement transfusion. In *Sobel & Wilhelm's* material from Lenox Hill Hospital in New York (1951) the figure is also 3 %. In Denmark *Scheel Thomsen (1954)* found 5 %. In 1951 *Diamond* and his team in Boston were able to report that their treatment of erythroblastosis was now so effective that only 2 % contracted kernicterus.

A relatively high frequency is reported by *Flamand Christensen (1954)*, who, among 21 cases of cerebral palsy admitted to a pediatric department from 1950 to 1953, found 8 with sequelae of kernicterus, 4 of them with erythroblastosis.

Of *Klingman & Carlson's* 675 cases of cerebral palsy (1937) 6.6 % survived icterus neonatorum gravis. Among mental defectives with cerebral palsy there were 6 % with isoimmunization, reports *Yannet (1949)*. *Evans (1948)* found that 7 % of 114 children with cerebral palsy had had kernicterus as a sequela to rhesus-isoimmunization.

Considered in relation to cerebral palsy on the whole, the problem thus is not particularly conspicuous. On the other hand it is remarkable that *Gerrard* in 1952 was able to gather information about 44 children who had survived neonatal kernicterus with erythroblastosis and 16 without. All these 60 children were born in hospital in Birmingham from 1927 to 1944.

Sequelae.

Kernicterus sequelae form a rather variegated neurological picture, which *Gerrard (1952)* has brought into some sort of order. He speaks of three groups: the grave cases with a fatal termination in infancy; the moderately severe, which survive the neonatal period but only with severe neurological symptoms consisting of generalized rigidity and pronounced dystonia. The third group represents the majority;

here there is little or no hypertonia, and the picture is characterized by abnormal movements of a choreiform, choreo-athetoid, or athetoid type. Often there is deafness. As the condition develops the picture varies. After the acute phase the child may seem normal. There may be slight opisthotonus and athetoid eye movements. Later the child is markedly hypotonic, after which there is often an ataxic phase, and at the age of three or four years the picture is dominated by the abnormal movements, hyperkinesiae. Clonic convulsions are rare. Reduction of intelligence is scarcely so common as was once assumed. The children are often emotionally sensitive. According to *Perlstein* paresis of upward movements of the eyes is frequently present.

Case No. 1.

Boy, R. S. K. Odense County and City Hospital, Neurological Dept. No. 9/1952, born April 8th, 1946, admitted Jan. 2nd, 1952, died Jan. 4th.

No known neuropsychiatric familial disposition. Second child of two. Four year old brother healthy. During whole pregnancy mother complained of tiredness, nausea, and sensation of pyrexia. She had no rubeola. Delivery was at proper time, no instruments used. Only brief and slight anaesthesia was given. Labour lasted 24 hours. Presentation vertex. At the close of the expulsion stage she had violent pain. The child was not in a state of asphyxia, was not icteric, and could take the breast. Weight at birth 3 kg. The child was well during first three days.

Four days after birth severe icterus set in, the child became limp, had convulsions in right arm and leg, lay with head retracted and flexed arms; occasional spasms in arms and legs, especially on right side. For a fortnight the child was very ill, then it improved.

From the third month there were frequent periods with pyrexia without demonstrable cause. During these attacks there were often clonic generalized convulsions, mostly on right side, lasting for a day or two, as well as constant generalized hypertonia, opisthotonus, lip-smacking, deviation of the eyes to the left, and a positive Babinski on the right side.

From the same age breast feeding was continuously impeded on account of rigidity and dyscoordination of the tongue.

From the fourth month constant generalized abnormal movements.

When 5½ years old, the child was admitted to the State Hospital, University of Copenhagen, Pediatric Dept.¹. The mother's blood type then was O. Rh.-negative, the patient's A. Rh.-positive. There was no rhesus antibody in the blood of the mother or the patient. The diagnosis was: sequelae of erythroblastosis foetalis. There was opisthotonus and generalized hypertonia with flexion of the knees and bilateral plantar flexion of the feet. The child was unable to hold its head up or sit or walk. On trying to walk it made rapid tripping foot movements with leg crossing. On trying to speak or make other complicated movements the hypertonia and opisthotonus were aggravated. Roentgenogram of the skull, Wassermann reaction, and toxoplasmosis reaction all negative. Intelligence judged to be normal. Hearing not severely affected. Parpanit and Artane administered without effect.

¹ Thanks are due to Dr. *Preben Plum* for free access to the case-record.

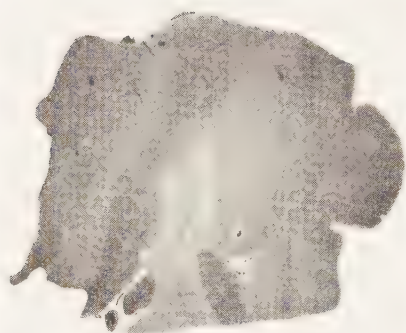


Fig. 1.

Case No. 1. Left corpus striatum.

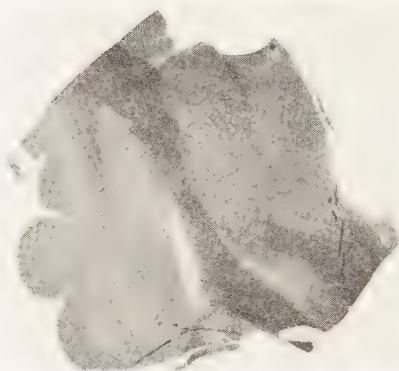


Fig. 2.

Case No. 1. Right corpus striatum.

When barely 6 years old the child was admitted to the Neurological Dept. of the Odense County and City Hospital.

He was thin, slightly cyanotic. Extensive caries of all teeth. Incessant hyperkinesiae of athetoid type. Head turned to the right and could not be turned to the front. Generalized muscular spasms with flexed elbows, clenched fists, opposed thumbs, flexed knees and bilateral plantar flexion of the feet. The abdominal reflexes were absent on the left side; positive Babinski on left side. He could not sit up and could only hold his head up momentarily. In a weak voice he could speak a word or two intelligibly.

On the day after admission he screamed loudly, perspired, was cyanotic and febrile. There was generalized hypertonia. He died on the following day.

Autopsy revealed the skull to be highly asymmetric with prominence on the right frontal and the left posterior side. Macroscopic examination showed nothing abnormal in peritoneum, pleura, suprarenals, the vena cava inferior and the femoral and portal veins, aorta, oesophagus, stomach, and intestinal canal. There was marked hyperaemia of the lungs, but no sign of pneumonia. On the posterior side of the heart just below the coronary sulcus there was a blood extravasation about 1×1 cm. in size under the pericardium. The heart otherwise normal; the liver was of normal shape, size and colour with a normal cut surface and consistency. There was severe hyperaemia. The pancreas normal. In the peritoneum just above the head of the pancreas there was a small superficial haemorrhage. The spleen was heavily charged with blood. The kidneys were congested. Urinary tract and bladder normal.

The brain surface, vessels, and membranes macroscopically normal. Spinal cord normal. Formalin was injected immediately after death.

Brain autopsy (K. A. Lorentzen).

Frontal sections of the brain revealed a distinct atrophy of the posterior part of the globus pallidus, which was much paler than normally. After staining of the preparations it was very evident that both globus pallidus and nucleus subthalamicus were much more difficult to stain than the surrounding tissues (Figs. 1 and 2). Otherwise, nothing macroscopically abnormal was observable.

Histological examination: In the globus pallidus (Fig. 3) very few nerve cells

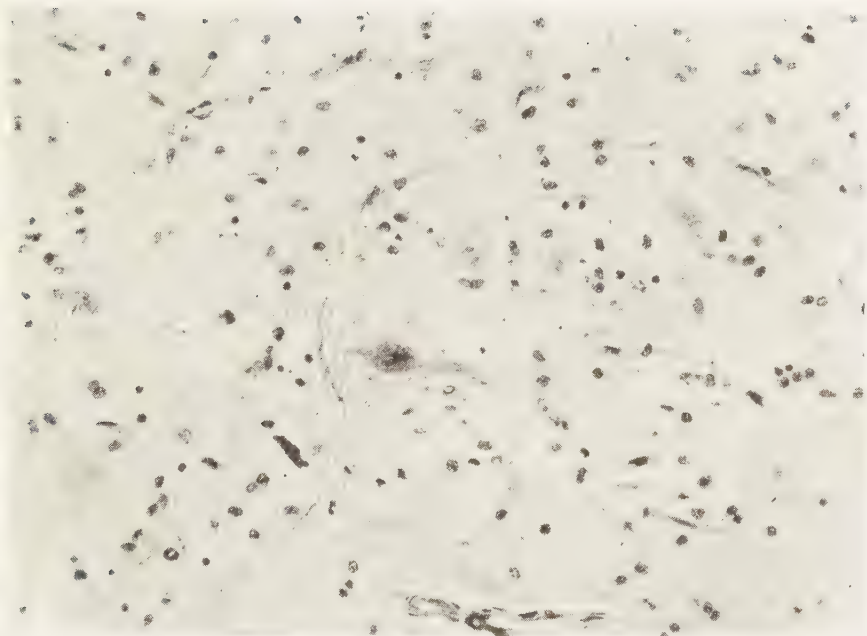


Fig. 3.

Case No. 1. Globus pallidus. Haematoxylin-eosin.

can be seen, the remainder of the tissue consisting of a loose network of glia branches in which are some glia nuclei. Specific staining of the glia revealed slight hypertrophy of the astrocytes, but no Alzheimer's glia forms anywhere. Within the atrophic area the vessels are somewhat sclerosed, but there is no cicatricial tissue. In the nucleus subthalamicus there is also a pronounced loss of nerve cells, but only insignificant gliosis. Many of the nerve cells are pale and there are a number of typical "ghost cells". It is striking that the adjacent parts of the putamen appear quite normal. Some nerve cells in the hippocampus are somewhat pale.

Nothing abnormal was observed in the blocks excised from the left and right sides of the cervical, thoracic, and lumbar regions of the spinal cord, the medulla oblongata, pons, mesencephalon, cerebellum, corpus striatum (including thalamus and hypothalamus), the parietal lobule, the central region, the superior frontal gyrus and the occipital lobe.

The stains used were: gallocyanin, haematoxylin-eosin, Bodian, toluidin-blue, Spielmeier's myelin, Globus and Penfield's impregnations. (Signed: K. A. Lorentzen).

Comments.

In symptomatology the case conforms closely to the literature reports of sequelae to severe kernicterus. Aetiologically it is one of rhesus incompatibility. *Gerrard* (1952) describes the characteristic details of these severe cases and states that a highly morbid condition (as in our case), developing rapidly concurrently with or shortly after the

onset of the icterus, has a grave prognosis. The same applies to the occurrence of clonic convulsions, the attacks of cerebral febrility and excessive perspiration. The early onset of hypertonia is another grave sign. Our patient presented all these symptoms. On going through his own cases and those in the literature *Gerrard* finds that the combination of early developed generalized rigidity and thermal instability in all cases involves death in early childhood.

The fateful hyperthermia was undoubtedly excited emotionally as a consequence of hospitalization and separation from the mother.

Case No. 2.

Boy, A. S. H., Odense County and City Hospital, Neurological Dept., No. 52/1952, born March 3rd, 1950, admitted Jan. 3rd, 1952, died Jan. 15th, 1952.

No known case of neurological disease in the family. The child was the first-born. The mother was well during pregnancy. Delivery was at the proper time and without anaesthetics and natural. Weight at birth normal (3,400 gr.). Amniotic fluid escaped May 1st, delivery came on May 3rd, having lasted only an hour or two. Immediately after birth the child was cyanotic and limp. He was examined by Dr. *Schondel* two days after birth; there was then incipient icterus which later became more pronounced and persisted for two or three weeks. Concurrently with the icterus onset there was respiration difficulty while suckling. In the early days the child was very restless and 17 days after birth the doctor found him still pale and limp.

When the child was one or two months old the head was observed to be bent backwards and the neck rigid. At six months there was a lack of tone in the back and the right arm was scarcely ever moved. The child screamed a good deal.

At 10 months the child was examined by the writer. The skull was narrow and long. The head was retracted and turned to the right. There was no paralysis of facial movements or of the tongue. Crying was natural. Little spontaneous movement in both arms with deficient grasping. Occasionally there were spasms in the left arm, which was extended and pronate in the left elbow. Hypertonia when the left elbow was flexed passively and when the right elbow was extended passively. Right biceps reflex hyperactive. Other arm reflexes absent. The hypertonia described was moderate; there was slight hypotonia when the other passive movements were made. The lower extremities were hypotonic apart from slight adductor hypertonia. The right patellar reflex was hyperactive, the left was normal. Both Achilles tendon reflexes absent in spite of good relaxation. Dorsiflexion of all toes on plantar irritation on both sides, but no typical Babinski. Abdominal reflexes absent.

The child smiled and could fix objects with the eyes. Lying supine it could not raise its head. When raised by the armpits the child hung limply, could not hold its head up, did not retract its legs.

When admitted to the Pediatric Dept. (Dr. *Flamand Christensen*) of the Odense County and City Hospital at this time, nothing abnormal was found on ophthalmological examination. Patient's blood type: A. Rh.-positive; mother's: O. Rh.-positive. Patient's serum contained no Rh.-subtype antibodies or irregular antibodies. Mother's serum contained no demonstrable Rh.-antibody.

There were repeated febrile periods without demonstrable cause.

When 17 months old the child was examined by Dr. *Scheel Thomsen*. There was now generalized athetosis. There were abnormal conjugate movements of the eyes of an athetoid type and only brief fixation. No strabismus. No nystagmus. The tongue could be extended but otherwise not moved. There was hypertonia of both arms, but it disappeared after repeated passive movements. The "voluntary" arm movements were compromised by athetosis. The abdominal reflexes were now present. The lower extremities were mostly hypotonic, but sometimes the tone increased with passive movements, to subside again while passive movements continued. The intermittent hypertonia was more distinct on the right side. The patellar reflexes were normal and equal. The Achilles tendon reflexes were active with a slight preponderance on the right side. There was a bilateral positive Babinski accompanied by athetoid movements. There was pronounced hypotonia of neck and back muscles so that the child could not hold up its head or sit up without support. The intelligence apparently was not reduced much.

When the child was 22 months old it was admitted to the Neurological Dept. He cried constantly and on the following day his temperature rose to 40.4° C. Gradually he had periods of screaming with paroxysmal generalized muscular spasm, opisthotonus and impairment of consciousness. On examination later, when the temperature was 38°, the findings were: On being raised the head fell limply. The eyes were closed. The eyeballs were centered or there was slight conjugate deviation to the left. Crying aphonic. Facial movements weak. No atrophy or abnormal movements of the tongue. Swallowing reflex normal. Only slight spontaneous movements of the arms, which are hypotonic. Abdominal reflexes present. Hypotonia in both legs excepting slight hypertonia in the adductors. Patellar reflexes slight, Achilles tendon reflexes normal, positive Babinski on left side, normal plantar reflex on the right.

Ophthalmological examination revealed nothing abnormal. Roentgenogram of skull and cervical spine normal.

The patient's condition became worse with a constant tendency to pyrexia and cyanosis. During crying periods there was sometimes fairly protracted apnoe with accentuation of the opisthotonus and tonic spasms in both arms with pronation, adduction and extension recalling decerebrated rigidity. There was a tonic neck reflex. Death occurred 12 days after admission under hyperthermia, cyanosis, and increasing respiration difficulty.

Autopsy: Skull dolichocephalic. Peritoneum, pleura, suprarenals, vena cava inferior and the femoral and portal veins, aorta, oesophagus, trachea, tonsils, throat organs, stomach, intestinal canal, pancreas, prostata, liver, bile ducts, kidneys, and urinary tract showed nothing abnormal. Lungs the seat of purulent bronchitis, discrete bronchopneumonia, oedema, and stasis. Heart: Foramen ovale open, measuring 1×1½ mm., wall in right ventricle rather firm and thickened, papillary muscles and trabeculae conspicuously coarse. Spleen: cut surface showed very firm, meaty tissue but normal pattern.

Microscopic examination of lung tissue showed acute bronchitis and small, purulent bronchopneumoniae. The splen tissue was hyperaemic and contained large quantities of deposited blood pigment. Suprarenal tissue normal without haemorrhage or necrosis.

Brain autopsy (K. A. Lorentzen).

Frontal sections revealed pronounced atrophy of the globus pallidus, which was present merely as a very narrow tissue stripe (Fig. 4). The tissue was so pale

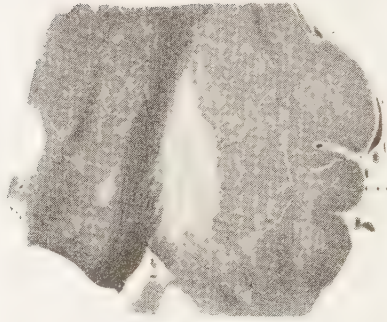


Fig. 4.

Case No. 2. Left corpus striatum.

as to give a first impression that the narrow stripe of tissue was part of the capsula interna and that the medial part of the putamen was the globus pallidus. After staining the atrophic stripe of tissue was quite distinct, the area being almost unstained. At the same time the nucleus subthalamicus was seen to be rather pale. Otherwise there was nothing macroscopically abnormal.

Histological examination: Few glia nuclei in the globus pallidus, localized to a fine glial network. No nerve cells observable. The glia cells somewhat coarse and usually slightly enlarged, but here and there there were also darkstained pycnotic elements. The vessels were normal. In the nucleus subthalamicus there seemed to be a moderate loss of cells, but no definite increase of the glia. Holzer staining failed to reveal any gliosis in the affected areas.

Nothing abnormal was found in the other representative blocks from the spinal cord and cerebrum (the same blocks as in Case 1). Staining methods as in Case 1. (Signed: K. A. Lorentzen).

Comments.

The aetiology of the icterus cannot be given in Case 2. Rhesus-immunization may be disregarded. As far as is known, there was no pyrexia in the neonatal period, so that an infectious origin is improbable. There was no prematurity, no syphilis, and the mother was not diabetic. There seems to have been moderate neonatal asphyxia. Thus, it may have been a matter of a hypoxic cerebral lesion, or the supposed cerebral hypoxia may have predisposed to kernicterus.

From the clinical aspect, too, this case fits well into *Gerrard's* group of severe cases with the early opisthotonus, febrile attacks and periods of generalized hypertonia (decerebrated rigidity). The athetoid movements seem to be less prominent than in Case 1, but it is often seen that they become maximal only at an age later than that at which patient No. 2 died.

DISCUSSION

The pathology of late cases of kernicterus.

Gerrard (1952) goes through 11 cases with brain autopsy on children who survived the acute phase of kernicterus. The children died at ages between 4 months and 6 years (Zimmerman & Yannet 1935, Bie-mond & van Creveld 1937 (2 cases), van Westrienen & de Lange 1938, FitzGerald, Greenfield & Kounine 1939 (2 cases), Sobel & Zucker 1940, van Bogaert 1947, Claireaux 1950 (2 cases), Gerrard 1952). To these I may add de Lange's 2 cases (1934 and 1936), Benda's 2 cases (1952), and the two cases described in the present article. The last six cases were also children of the age mentioned.

Every one of these 17 cases had pathological changes in the globus pallidus. The lesions were usually macroscopic, as was not the case with any changes which may have occurred elsewhere. Under the microscope, too, the changes in the globus pallidus were more pronounced than elsewhere.

In the 12 cases where mention is made of it, changes were found in the nucleus subthalamicus. Mostly they were pronounced, but generally not so massive as in the globus pallidus. There were also changes in the putamen, but by no means in all cases and usually less marked than in the localities referred to. In a few cases marked lesions were found in the nucleus caudatus, but as a general rule this part of the neostriatum, too, is only slightly affected or not at all.

The hippocampus with fascia dentata is fairly often the site of distinct lesions. Changes in the thalamus, the red nucleus, substantia nigra, the inferior olive and the dentate nucleus do occur, but rarely. No examination seems to have been made of the nerve paths between the ganglia.

In agreement with what was observed by Pentschew (1948), Evans & Polani (1950), and Gerrard (1952), the perusal of the literature compared with our own two cases thus shows that the lesions in the globus pallidus and nucleus subthalamicus are constant and the most pronounced, whereas there are only infrequent changes in the neostriatum, and that these are less prominent. The hippocampus is often affected. Changes elsewhere are rare.

Histologically, there is an absence or severe loss of nerve cells. This is a constant finding, almost always stated to be most pronounced in the globus pallidus and nucleus subthalamicus. Very often there is also demyelination of the same regions, less pronounced in the putamen and in the caudate nucleus. Gliosis is sometimes seen, but mostly it is but little pronounced and, as in our cases, may be wholly absent.

The neurological symptomatology in late cases of kernicterus with autopsy.

The symptomatology in late cases of kernicterus is described in detail e.g. by *Pentschew, Lande (1948)*, *Evans & Polani* and particularly thoroughly and clearly by *Gerrard*. The severe cases leading to autopsy in infancy— are especially characterized by a severe onset followed by the development of generalized and extreme rigidity with head retraction and opisthotonus, twitching movements of the limbs, irregular fever and bouts of excessive sweating. As pointed out by *Biernard & van Creveld, Filtz-Gerald et al., van Bogaert, and Gerrard*, the hypertonic posture recalls the decerebrate (or decorticate?) primate. The head is thrown back, the arms are adducted (or slightly abducted) in the shoulders and flexed in the elbows, the fists are clenched, the thumbs in opposition. A posture like this was seen in our Case 1 (page 267) and terminally in Case 2 (page 271), where the attack resembled decerebrate rigidity. During an examination of Case 2 (page 270) there were intermittent tonic spasms with the same posture (extension and pronation), but localized solely to one arm. It is characteristic that the rigidity occurs intermittently and that it is often provoked by handling the child or by the typical bouts of fever. Frequently, however, the rigidity is constantly present throughout, or it gradually becomes so. Generalized rigidity was described in all the 17 cases with autopsy.

The abnormal, athetotic movements do not set in until after about the fourth to the twelfth month. They disappear during sleep.

The athetotic movements were described in only seven of the 14 cases (from the autopsy material) in which the clinical description was adequate. Of these seven, six were between one and six years old at death, whereas one was nine months old. Of the seven without athetosis, on the other hand, six were between three and six months, one was nine months. This positive correlation between age at autopsy and the occurrence of athetosis must be borne in mind when attempting to correlate the symptomatology with the pathological findings.

In more moderate cases hypotonia is a frequent finding, observed at about the third month and persisting or disappearing after six months to two years. In the— severe—cases leading to autopsy, hypotonia seems to be rare; at any rate it is mentioned only by *de Lange (1934)* and in our Case 2, where it was observed from the sixth month until death at the age of 22 months. In this case there was also intermittent and localized hypertonia. On the whole, fluctuating tonus is often described.

Correlation of clinical and pathological findings.

It would seem to be a reasonable assumption that the dominating disturbances of the motor function observed in all cases—rigidity and athetosis—are caused by the only lesions which are constantly present, i.e. those in the globus pallidus and the subthalamic nucleus. How does this compare with other experience, clinical as well as neurophysiological?

Designated as *status dysmyelinisatus* (Vogt & Vogt) a number of cases have been reported (Fischer 1911, Vogt & Vogt 1920, Schaparow *et al.* 1928, Laruelle & van Bogaert 1929, Ammosow 1931, Kreyenberg 1931, Winkelman 1932, Papez *et al.* 1938, Balhasar 1939) with severe changes in the pallidum and no changes, or only insignificant ones in other parts of the basal ganglia. Clinically, there is a striking resemblance to late cases of kernicterus: in all cases there is generalized rigidity and in all cases except Winkelman's, athetosis or torsion dystonia. All cases (except Fischer's) were congenital and in all cases except two (Kreyenberg and Fischer, who state nothing about the birth) there were parturition complications. In Laruelle & van Bogaert's and Balhasar's cases there was neonatal icterus.

It seems then that as a rule "status dysmyelinisatus" agrees closely with late cases of kernicterus as regards both the locality of the pathological findings and the motor symptoms, though no special mention is made of changes in the subthalamic nucleus. The cases appear to be of neonatal and presumably postasphyxial origin; possibly some are actually late cases of kernicterus.

In the so-called *status marmoratus* both the putamen and the globus pallidus are regularly the site of pathological changes. The same often applies, though not always, to the nucleus caudatus (Malamud 1950). There is often athetosis in these cases. Malamud believes that a prerequisite for the appearance of athetosis is that the nucleus caudatus is bilaterally involved. Statistically his conclusion seems somewhat hazardous, and, however that may be, it is contradicted by the above observations.

In paralysis agitans and sequelae of carbon monoxide poisoning the globus pallidus is affected. In cases of juvenile paralysis agitans Hunt (1917) has found a progressive atrophy of the pallidal system. Clinically, these cases are characterized by rigidity and tremor. The typical tremor at rest is presumably caused by lesions in the substantia nigra (Davison 1942).

Both clinically (e.g. Wulff 1932, Whittier 1947) and experimentally (Whittier & Mettler 1941), localized pathological changes in the nu-

cleus subthalamicus induce abnormal movements in the form of counterlateral *hemiballismus*. Hemiballismus is not observed in kernicterus. This agrees well with *Whittier & Mettler's* experiments on rhesus monkeys; they found that the destruction of the nucleus subthalamicus does not lead to ballismus when the pallidum or its connection with the nucleus subthalamicus is destroyed.

Experimental bilateral, isolated lesions of the globus pallidus in monkeys (*Ranson & Berry* 1941, *Kennard* 1944) have not led to observable abnormalities, although in the case of large lesions *Richter* (1945) found a picture recalling the Parkinsonian syndrome in man, but without tremor.

With regard to the function of the neostriatum, a number of experimental observations (*Mettler & Mettler* 1941, 1942, *Kennard* 1944, *Liddell & Phillips* 1946, *Lindsley, Schreiner & Magoun* 1949) suggest that the neostriatum exerts an inhibitory function on other motor areas. The function of the pallidum seems less certain. *Mettler* (1945) concludes that the pallidum sensitizes the organism to proprioceptive stimulation. *Rhines & Magoun* demonstrate (1946) facilitation of cortically induced motor responses by stimulation of the ansa lenticularis, i.e. efferent paths from the globus pallidus, to which they ascribe an activating influence on the facilitatory area in the reticular formation. In this they see an explanation of the Parkinsonian-like state produced by experimental destruction of the globus pallidus (*Richter* 1945), especially an explanation of the hypokinesia. It is surely doubtful, however, whether the hypokinesia can be regarded as a "negative" symptom; it would be more likely to see it is a secondary phenomenon, considering the rigidity as the primary symptom and as a "positive" symptom whose appearance must be due to abolition of an inhibitory function. This seems to be in accordance with the ideas of *Kinnier Wilson* (1925).

Magoun et al.'s demonstration (1946) of the existence within the reticular formation of a large facilitatory area and more posteriorly and laterally a bulbar inhibitory area has thrown new light upon decerebrate rigidity. As stated above, the rigidity in late cases of kernicterus is remarkably similar to experimental decerebrate rigidity. It would therefore seem reasonable to assume that it is due to abolition of inhibitory impulses from the globus pallidus (and nucleus subthalamicus?) to the facilitatory area of the reticular formation. This is supported by the fact that important efferent pathways lead from the globus pallidus and nucleus subthalamicus to the reticular formation (*Ranson et al.* 1941, *Meyers et al.* 1948). Possibly there is also an interruption of inhibitory impulses from the nucleus caudatus via the putamen (*Lindsley, Schreiner & Magoun* 1949).

As regards the pathogenesis of the athetoid movements, it seems important to point out that, in contrast to the rigidity, they are not present from the onset, but only appear later. In the autopsy material, those over nine months of age at death had athetosis, those under nine months had not. There was no difference between the two groups with regard to the localization of the pathological changes. As age would thus seem to be the critical point here, it seems fair to conclude that a developmental factor is a prerequisite of athetosis. According to *Lassek* (1948), myelinization of the pyramidal tract takes place from the ninth to the 24th month. At just about the ninth month the normal child (*Gesell & Amatruda* 1951) starts to use the fingers in a rather complicated way (*Gesell*: "the exploratory index finger"). It is well-known from other spheres of experience that the normal performance of highly skilled movements is conditional upon the intact function of the pyramidal tracts. It must therefore be reasonable to state that the occurrence of athetosis is conditional upon intact pyramidal tracts (including their origin in the cortex). This is in harmony with the clinical experience (*Wilson* 1925) that the athetosis disappears on the paretic side if a patient with double athetosis gets hemiplegia. It is also in accordance with the fact that athetosis disappears or decreases after anterior chordotomy (*Putnam*) or removal of area 6 (*Horsley, Bucy & Buchanan* 1932, *Bucy* 1948).

It may perhaps be permissible to say that athetosis "is due" to attempts at performing complicated movements in the presence of a certain type of (decerebrate?) rigidity.

Is there an area the lesion of which is a prerequisite for the development of this rigidity and thus for athetosis?

In his exhaustive study of the literature *Carpenter* (1950) arrives at the conclusion that double athetosis—with or without torsion dystonia—most frequently is a consequence of bilateral lesions in the striatum, especially status marmoratus, and that it may appear as a result of bilateral status dysmyelinisatus of the globus pallidus. He furthermore considers that status marmoratus of the striatum does not inevitably result in double athetosis, although such instances are rare, and that double athetosis may appear without demonstrable pathological change in the striatum and globus pallidus, but such cases also seem to be rare.

In his study of 15 cases of status marmoratus *Malamud* (1950) found that the globus pallidus was always affected, but usually less than the putamen. *Jacob* (1925) stated: "... athetoid movements in adults are found only in cases (of status marmoratus) in which there are lesions in the pallidum."

As the globus pallidus—as we have seen—is always affected in late

cases of kernicterus with athetosis, it looks as if pathological changes in the globus pallidus were a *conditio sine qua non* for the appearance of athetosis.

However, according to *Bucy* (1942) there are cases with athetosis (without changes in the globus pallidus?) associated with lesions in the ventrolateral nucleus of the thalamus (*Schuster*) or neostriatum (*Alexander*). Hemiathetosis is occasionally seen in cases with lesions of the brachium conjunctivum (*Carpenter*).

On the basis of the present material it is not possible to answer the question whether the inhibitory impulses which from —and via?—the globus pallidus affect the bulbar and spinal motor neurons, pass via the ventrolateral nucleus of the thalamus to the precentral cortex (*Bucy*) or via the reticular formation (*Benda & Cobb* 1942, *Magoun* 1946) and reticulospinal paths. The circumstance that the rigidity—which is at the root of the athetosis—is present before the pyramidal tracts are mature seems to argue in favour of the latter possibility.

SUMMARY

The clinical and pathological findings in two late cases of kernicterus are described in detail and compared with 15 cases in the literature. The age at death was between 4 months and 6 years. The symptomatology is characterized partly by a generalized rigidity, present from the onset and recalling experimental decerebrate (decorticate?) rigidity, partly by athetosis, which appears later and which was only present in those patients who died at the age of nine months or later.

Lesions in the globus pallidus and in the subthalamic nucleus were found in all the 17 cases and were more pronounced than lesions in other localities. There are not always lesions in the neostriatum. The hippocampus is often affected. Changes elsewhere are relatively rare.

Pathogenetic problems are discussed. It seems to be a reasonable assumption that the generalized rigidity is the result of abolition of inhibitory impulses from the globus pallidus (and nucleus subthalamicus?) to the fascilitatory area of the reticular formation. The circumstance that the athetosis develops in the same age as that in which the pyramidal tracts mature and highly complicated (digital) movements develop (in the normal child) confirms other observations which argue that intact function of the pyramidal tracts are a prerequisite of athetosis.

Status dysmyelinisatus of the globus pallidus, which most often seems to be of neonatal and post-asphyxial origin, is associated with

the same type of generalized rigidity and athetosis as the late cases of kernicterus mentioned. Status marmoratus is possibly associated with athetosis only when the globus pallidus is involved. It is therefore probable that another *conditio sine qua non* of athetosis is lesion of the pallidum.

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THE PHANTOM LIMB EXPERIENCE IN RELATION TO THE PROBLEM OF ANOSOGNOSIA

By

VILLARS LUNN

The phenomenon of anosognosia has been treated with steadily increasing attention both by neurologists and the psychiatrists during the last 10-15 years. The subject has been discussed in detail in numerous case histories and in a number of monographs. Consequently, it may be said that both the symptomatology and the frequency of anosognosia as well as its relationship to lesions of the interparietal region of the minor hemisphere have been extensively investigated and elucidated.

Nevertheless, we must realize that the fundamental problem of anosognosia remains unsolved: the psychological mechanisms which are the bases of the hemiplegic patient's subjective experience of an intact body are still enigmatic and baffling to us. We have still no knowledge of the psychological background of the phenomenon that such a patient actually *perceives* that he moves the paralyzed limb, that he, with an unshakable conviction, *denies his being an invalid*.

For this reason it is natural, in order to reach an understanding of this phenomenon, to consider other deviations from the normal body experience or body consciousness. With this aim in view I have made a detailed psychological analysis of the phantom limb experience on the basis of case histories from 235 amputated patients.

Among these patients *90 per cent* stated to have some kind of illusory sensation or experience from the amputated limb. The following elements of the phantom experience of these patients have been analyzed: The "structure", position, and motility of the phantom limb and its relationship to the artificial limb and the stump. Further, the statements made by these patients with regard to temperature and pain and as to the degree of "reality" attached to the experience. Finally, all the patients have been subjected to an intensive psychiatric and psychological study by a number of projective tests (including the

Rorschach) and intelligence tests. The results obtained have been subjected to statistical treatment, an analysis having been made of the correlation and interdependence of the individual elements.

With regard to the question of the pathogenesis of the phantom experience the results of the investigations support the view that *it is impossible to maintain the classic "sense-psysiological theory"*. According to this theory the continuous irritation of the severed nerve trunks in the stump will release afferent impulses which are projected outwards to the region originally innervated by these nerves and thereby cause the patient to perceive the amputated limb as actually existing.

However, it is not the question whether the phantom experience is a phenomenon independent of peripheral impulses. There can hardly be any doubt that physical stimulation of the nerve ends in the stump *influences* the phantom experience. The question is whether the phantom experience as such is *identical* with the projected afferent nervous impulses. And to this question the reply is in the negative.

Certain characteristics of the phantom phenomena experienced by amputated patients can hardly be explained as caused by afferent impulses. However, they are readily accounted for on the assumption that the phantom experience is based on a mechanism that we, for the time being, might describe as a "superior cerebral mechanism", viz.:

(1) The distribution of the peripheral innervation rarely or never manifests itself in the phenomena experienced by the patients. The patient does not for instance perceive the part of the extremity, innervated by the ulnar nerve, as being present, but the perception corresponds to the patient's *idea* of "a hand", "a foot", etc., according to the distribution of the cortical representation. If we summarize the statements made by all the patients as to the part of the limb they perceive as present, or perceive with the greatest intensity, and if, on the basis of these statements, we draw an "average phantom limb", this figure will display a striking likeness to the "homunculus" illustrating the cortical motor and sensory representation. It is consequently *the latter* that is reflected in the phantom experience, while the distribution of the peripheral innervation does not manifest itself in the phenomenon, neither qualitatively nor quantitatively.

(2) It is well-known that in many patients the phantom limb goes through *regressive changes*, generally in the form of a gradual shrinking, which in the course of time causes the "hand" or "foot" to approach the stump. It is difficult to account for this phenomenon as being caused by the projection of afferent impulses. But, it is readily explained by the assumption of a cessation of actual sensory impressions from the periphery. In consequence the awareness of the fictiti-

ous limb is then determined by the cortical distribution, that is of the "cortical" or "central" shape of the limb.

(3) In a number of cases the phantom limb is felt to have "*stiffened*" in the position the limb took up at the moment of amputation. In these cases the patients have been conscious at the moment of the accident; the amputation has meant a severe psychic trauma. It seems more natural to account for this fixation in "the last position" by affective psychogenic mechanisms than to "explain" the phenomenon as "un simple phénomène physiologique".

(4) More than half of the patients declare that they *feel they are able to move the phantom limb*. The physiological "explanation" of these kinesthetic sensations is that the muscles left on the stump contract when the patient "imagines" a movement of the phantom limb. This theory is invalid, however, if only for the reason that it cannot explain, why, for instance, the "fingers" may be moved also after amputations of the humerus in which all muscles involved in such movement have been removed.

(5) *Pain and paresthesia of the phantom limb* are undoubtedly frequently released through irritation of the nerve ends of the stump. It is a fact, however, that in 80 per cent of the cases the awareness of the phantom limb is independent of the patient's experiences of pain or paresthesia of the limb. Furthermore, it is possible to make the pain in a phantom limb disappear without the simultaneous disappearance of the phantom experiences per se, while—vice versa—the pain in some cases persists throughout all peripheral measures. These intractable pains are described by the patients as pressing or squeezing and are distributed uniformly over all parts of the "hand" or "foot". They do not appear to have any parallel in any pain caused by external influence on the intact limb and they are presumably of *central origin*.

(6) Finally it may be mentioned that a number of these patients experience *tactile sensations corresponding to particular incidents*: the patient *feels* that his "foot" becomes wet, when he steps into a puddle with his artificial limb; he *burns* his "instep", when his artificial limb touches nettles; he *feels relief*, when scratching the artificial limb at a place corresponding to the itching part of the phantom limb. Such sensations cannot be explained on the basis of the "peripheral" theory—because in none of these cases has the stump been subjected to any adequate stimulus. These examples show more clearly than any other feature of the phenomenon that the phantom-limb experience is influenced by central psychological mechanisms, as it seems to some extent independent of afferent impulses from the periphery.

We are now faced with the task of analyzing the nature of the element in the genesis of the phantom experience which we have hitherto described neutrally as "the superior, central mechanism".

We may ask whether this central mechanism is of a sensory *or* of a conceptional character. But it will soon be realized that this is not the right way to approach the problem; there is no doubt, whatever, that the patient's awareness of his phantom limb being touched or moved has the character of a sensory impression as distinct from something reproduced or remembered—but it is equally certain that no stimulus has been applied to the specific sensory organs in this case. The phantom experience must therefore be considered to illustrate the psychologically identical nature of sensation and concept. The central element of the phantom experience must consequently be considered an ideational process which appears with the clarity and precision of sensation and consequently is mistaken for a sensation by the patient; that is, a hallucinatory experience, a body hallucination.

This conclusion leads us to the question as to the factors which in the cases of amputated patients favour a hallucinatory way of experiencing.

The answer to this must, in my opinion, be that the cessation of the normal differentiated peripheral impulses is one of the factors that is responsible for the "hallucinatory" body experience in these mentally normal patients. The cessation of the normal afferent impulses is equivalent to the weakening of the sensory element which—within other fields of sensation—is well-known to favour hallucinatory experiences—confer the occurrence of visual hallucinations in the dusk, the frequent occurrence of auditive hallucinations in deaf persons, the hemianoptic, optical hallucinations, etc. The hallucination is consequently—at any rate with regard to some of the forms of this polymorphic symptom—to be considered as a symptom caused by the cessation of stimulation and not caused by actual stimulation.

Finally, we must ask: What is the explanation of the highly *varying intensity* with which the phantom experience occurs in amputated patients? How should we account for the fact that it is completely lacking in about 10 per cent of such patients, that it only occurs sporadically and fragmentarily in about one third, but with maximum intensity in about 30 per cent, and that kinesthetic sensations lack in about half of the cases, etc.?

The answer to this question, as obtained from the psychological analysis of the patients and particularly from the Rorschach psychograms, must be that the observed *variation* in the intensity and differentiation of the phantom experience is, at any rate to some extent,

the result of constitutional, mental characteristics of the patients concerned.

We have consequently reached the opinion that *the phantom experience is a complex mental phenomenon, which may be described as an act of imagination, in which the image appears with the clarity of a sensory phenomenon, but which in addition contains elements of "genuine" sensory perception (pain, paresthesia). The occurrence of this body hallucinatory experience is conditioned by the cessation of the normal afferent peripheral impulses, but the varying intensity of the phenomenon must be considered to be the result of constitutional mental characteristics in the patient in question.*

It is possible that this view of the genesis of the phantom experience will provide us with a key to the understanding of the problem of anosognosia from a psychological point of view.

The amputated patient has a *feeling* of having retained the amputated limb, but he is at any time able to correct this feeling, without resorting to the use of other sensory organs. *He recognizes his defect even if he does not perceive it.*

In contradistinction to this the hemiplegic patient, suffering from *anosognosia sens. strict.*, does not only *perceive* his body as being intact in spite of the somatic defect, but he also *denies* the existence of the defect. The essential element in these cases is the patient's lacking recognition of his actual "somatic situation". He ignores or neglects the paralysis (*anosodiaphoria*); he claims—and feels—that he moves the paralytic limb (*anosognosia sens. strict.*); he is convinced that he lacks one half of his body (*asomatognosia*) or that the paralyzed limb does not belong to him, but to somebody else, or, in some cases, is somebody else (*dyssomatognosia*).

These patients also experience phantom phenomena, but unlike amputated patients, patients with anosognosia are convinced of the objective reality of the fictitious experience.

In order to be able to analyze the factors responsible for this difference in the attitude towards the phantom experience, I have performed a detailed neurological and psychological examination of altogether 23 patients, suffering from cerebral hemiplegia and denial of the somatic functional disorder.

In all 23 cases the patients suffered from a left hemiplegia, following a *lesion of the minor hemisphere* (hemorrhage, thrombosis, tumor, contusion). In 9 cases post-mortem examinations of the brain have been made, in all of them disclosing extensive lesions involving considerable parts of the minor hemisphere, including the interparietal region and/or radiatio thalamo-parietalis and/or thalamus and/or corpus callosum.

The following functions were made the object of a particularly careful examination: the motility and sensibility of the limbs, the visual field, the autopsychic and allopsychic orientation, attention and perception, intensity of consciousness, emotionality, and affectivity, contents of memory, and power of retention, and finally the function of speech and the gnostic function. The result of the examinations cannot be given in full here, but three observations of fundamental significance should be mentioned:

In the first place it is a general rule that in the cases in which the patients state that they are aware of movements of the paralyzed limbs, severe sensibility disorders will also be observed. In these patients there is either total anesthesia-algesia with loss of the position sense or such a severe hypesthesia that the patient is not aware of it when being touched. (On the other hand the actual anosognostic experience, i.e. the denial of the paralysis, may very well be present in spite of an intact superficial sensibility—but in such cases there are no kinesthetic hallucinations).

In our discussion of the phantom experience of amputated patients we concluded that this phenomenon should be considered to be conditioned by the cessation of real peripheral sensory impulses. It is reasonable to assume that *the anesthesia in the hemiplegic patients is the corresponding factor, conditioning the hallucinatory experiences*. (This does not mean that sensibility disturbance is a *sufficient* condition of the occurrence of anosognosia—as might be realized merely from the fact that the phenomenon is relatively rare even in case of *total* hemiplegia and anesthesia).

In the second place it generally holds true that the *total cessation of function is more easily disregarded than partial defects*. Patients with a total paralysis of the left leg and a moderate paresis of the left arm will firmly assert that there is nothing the matter with the leg while admitting to some difficulty in moving the arm.

In the third place all the patients are—besides suffering from the somato-gnostic disturbance—characterized by *general mental deviations*—whether of a severe or mild degree. A slight clouding of consciousness is often observed— in some patients increasing to moderate somnolence or sopor. The mood is in about half of the cases characterized by a certain uncritical euphoric cheerfulness. And finally all the patients display signs of a general intellectual reduction, manifesting itself chiefly by a somewhat reduced power of retention.

Impairment of the consciousness is most pronounced in the patients in which the anosognosia is *without* accompanying kinesthetic sensations. In patients with anosognosia sens. strict., i.e. in patients

who claim that they *feel* that they move the paralyzed limb, both the clouding of the consciousness and the general mental reduction usually are not very pronounced.

The *conclusion* drawn from the described observations discloses that for the appearance of the anosognostic experience a *combination* of four "elements" is required: First, a lesion of the interparietal region of the minor hemisphere, second, a total loss of sensibility—or severe impairment of the sensibility—in the limb involved; third, total cessation of motor function—or severe disturbances of the motor function—of the limb involved; and, fourth, an impairment of the consciousness and a general mental deterioration of a varying degree. Anesthesia appears to be a requisite to the "fictitious" kinesthetic sensations, while the mental deviation is presumably the most important factor among the reasons for the denial of the defect *per se*.

It is well-known that most of the researchers who have tried to give an "explanation" of anosognosia and similar conditions have ascribed the phenomenon to a lesion of the "body image", a defect of "*l'image de notre corps*". In this connection we may mention works by Head, Pick, Schilder, Hoff, Conrad and Lhermitte and his school. These authors—and a number of others—have with their valuable contributions widened our knowledge of the symptomatology of the somato-gnostic disturbances. Nevertheless, it should be realized that the definition of the concept of "body image" is still rather vague. By some authors it is used merely in an *illustrative* manner as "ein Raumbild, das jeder von sich selber hat" (Schilder)—"une image, un schéma tridimensionnel de notre corps, effleurant au seuil de notre conscience" (Lhermitte). By others the body scheme is viewed as a purely "formally-logical concept", a "standard" against which the sensory impressions are measured—and others again consider it to be a *physiological mechanism*, a function of special associative systems. Finally the word is also given a purely *psychological meaning*, and from this point of view the "body image" is defined as the "sum" of special images of conception and memory, as a "knowledge" about one's own body, as an "unconscious" psychic content.

As matters are at present, it must be realized that the concept of the body scheme has no actual meaning. For this reason I have in this work deliberately avoided the use of the term, and have instead endeavoured to approach the phenomenon of anosognosia on the basis of a multi-dimensional causal description. This method has the advantage of avoiding the introduction of unknown or hypothetical concepts while being based solely on phenomena known from other psycho-pathological conditions.

But it must be acknowledged that this method does not result either in a fully satisfactory solution of the problem of anosognosia from a psychological point of view. It is presumably impossible to reach such a solution on the basis of the terms and concepts of the "atomistic", "elementary" psychology. Among the "elements" which make up our normal body experience or body consciousness we may mention: a "*knowledge*" of the material properties of the body, visual *conceptional images* of the body or parts of it; *actual sensory impressions* which may either be "external", i.e. experienced through exteroceptors, or "internal", i.e. experienced through interoceptors; and finally *affective components*, as they express themselves e.g. in our vanity. But it should be emphasized that our normal experience of phenomena as the mere existence of our body, its dimensions, continuity, and normal functions is something else than and something more than the "*sum*" of these elements,—because all the elements may be intact, and the body may nevertheless be experienced as being defective; or although certain "elements" are "lacking", the body and its function may be experienced as being intact. We do not know what this "something else" may be. We may describe it as a "gestalt-function", an "unconscious" global experience of the body and its function, in which the experience of the entity is superior to and dominates the detail. And we may assume that the interparietal region of the minor hemisphere is of particular importance to this gestalt-function. But we must realize that hereby we are introducing new hypothetical concepts, and that we are still awaiting the solution of the enigma of anosognosia.

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ON PATHOLOGICAL RETARDATION OF MOVEMENT

(*A plea for closer attention to the speed factor of movements*)

By

G. H. MONRAD-KROHN

It is indeed surprising that the speed of movements, in contradistinction to the strength of movements, is so rarely recorded in neurological publications. Presumably, then, this factor is not given any closer attention in the clinical observation. And yet alterations in the speed factor of movements are of the greatest importance both for diagnostic purposes and for the purpose of obtaining necessary data for the assessment of any motor invalidity. In both respects I should term the observation of the speed of movements an indispensable link in the clinical examination.

The two fundamental properties of any movement are:

- (1) The *strength* of the movement concerned and
- (2) The *speed* of the movement.

The maximum values of both these properties should always be ascertained. The record of the strength only represents a half statement. One need not have recourse to "the noble art of self defence" to illustrate this, as any one knows that a quick nimble fighter may often out-box a much stronger slow slugger. Also for needlework, writing, typing, playing the piano, the violin, and many other instruments the speed of the movements is just as important as their strength—or even more so. Whilst in many such occupations a slight loss of power may cause no appreciable invalidity, a pathological retardation may cause a serious handicap amounting to complete incapacity. (That in some forms of heavy labour the opposite may obtain by no means refutes this).

Thus it is obvious that a mere retardation of movement may represent an important incapacitating factor, irrespective of the strength of movement—so obvious in fact that one ought perhaps to apologize for mentioning it, if one had not so surprisingly often seen this quality of motor function entirely overlooked.

Now it may perhaps be objected that as a rule a retardation of movement is accompanied by loss of strength,—and vice versa. This, however, is not entirely true.

It must of course be conceded that retardation may indeed even be the consequence of the loss of strength. When a professional weight lifter in a circus lifts objects of stupendous weight, just within the limit of his capacity, the movement is as a rule carried out very slowly. In the same way weakened muscles are contracting very slowly when loaded up to the limit of their reduced strength. But apart from this “secondary” kind of retardation, characteristically seen in peripheral motor lesions, there are *numerous conditions, mostly of central origin, in which the speed of the movements is reduced out of proportion to the loss of their strength*. To the experienced clinical observer, who makes a point of always examining the speed of movements, it is a commonplace observation that many pareses of central origin,—of the “pyramidal” as well as of the “extra-pyramidal” type—are characterised by this dissociation between a markedly impaired speed of movement and a comparatively or entirely unimpaired strength of movement. An isolated retardation may appear as an initial sign,—and also as the only remainder of a central motor lesion, when recovery takes place.

The observation of the speed of movements may thus furnish valuable diagnostic information, the dissociation just described pointing to a central origin of a motor impairment. Any pathological retardation constitutes in itself an element of incapacity, which for some occupations may be entirely frustrating.

That very pronounced pathological retardation may in itself cause an unsteadiness of gait, which may be classified as “*pseudo-ataxia*”, I shall only just mention here. The necessarily limited space also prevents me from discussing the pathogenesis of the retardation, which need not always be the same. Let me only mention that, in many cases at least, there seems to exist a relation between the retardation and the resistance or rigidity elicited by passive movements. This applies equally to the moulding (“pyramidal”) and the plastic (“extra-pyramidal”) kind of rigidity.

Nor shall I deal with other changes of speed (e.g. acceleration) than the all important retardation.

That admittedly there may be individual differences in the rapidity of movements in normal individuals (genetic or acquired, heavy labour developing slow movements, piano-play quick ones) is no reason whatsoever for overlooking the important element of speed.

For the sake of completeness it should be mentioned that when a

certain movement causes pain, it may on this account alone become very slow without any lesion of the nervous system.

On the other hand I should like to point out that a pathological retardation of *voluntary* movements need not be accompanied by a corresponding retardation of *reflex* movements. In fact I have myself observed a young man with a pronounced spastic paraplegia and a marked retardation of voluntary movements, who surprised me by asking if he might continue boxing. On shadow-boxing (which I have kinematographed) he utilised his myotatic reflexes in such a way, that whilst his ordinary gait was slow and strongly pathological, his foot work in boxing to a non-expert in this noble art seemed fairly efficient and unimpaired but for an increased adductor reflex with a tendency to adductor contracture.

In concluding I should like to express the wish that the speed of movements and particularly the pathological retardations be given more attention than hitherto, first and foremost in the clinic, but also in experimental work on the motor system. True, it may be difficult or impossible to make an experimental animal show the maximum speed of the various movements. Still it would probably be easy to get an impression of a pathological retardation when very pronounced. At any rate it should also in experimental reports be recorded whether one has succeeded in getting an impression of the speed factor or not. On the whole it remains a desideratum in this as in other respects that the examination of experimental animals and the recording of the findings should, within the limits of the possible, *try* to approach the completeness of the clinical examination and description of the human patient.

ON DYSAEMIC MYELOPATHY

By

C. J. MUNCH-PETERSEN

The neurologist who for the last decades has been confronted with the perplexing problems of multiple sclerosis might be in need of the warning "Steady!" uttered when difficulties arose by Dickens' immortal Captain Cuttle.

It is perhaps to go too far to argue that both the clinical and historical diagnosis of multiple sclerosis is purely hypothetical; that after all we do not know what multiple sclerosis really is; and that, consequently, the attempts with recent years to approach the aetiological and therapeutical problems by means of metabolic, geographical, and statistical methods must, to some extent, be regarded as premature.

It is of course a commonplace to state that, even though it may be difficult to make a diagnosis of multiple sclerosis, the clinician nevertheless is rather confident in making it.

We must, however, admit of the possibility that the aetiological basis of the clinical entity constituting what we call the multiple sclerosis may be heterogeneous.

The clinical diagnosis may naturally be verified at autopsy, by the demonstration of plaques. But even in such circumstances we are not allowed to infer anything as to the aetiological factors of the condition.

Endogenous factors may play a role as to the response to various pathological agents in the central nervous system.

The "classical" plaque, sharply limited, with its almost selective degeneration of the myelin sheaths and the exorbitant proliferation of fibrillar glia shows transitions to the less sharply defined sponge-plaque. Here degeneration of the myelin sheaths as well as of the axis cylinders are encountered together with insufficient proliferations of the fibrillar glia.

It is not, in my experience, possible to correlate the nature of the clinical changes of multiple sclerosis with that of the plaques.

In fact, the sponge-plaque does not differ in principle from the spongelike degenerative changes found in the spinal cord in case of pernicious anaemia.

The question arises whether a dysaemic factor (probably due to deficiency of the antipernicious anaemia principle) is able to bring about the clinical picture of multiple sclerosis with plaque formation in the central nervous system.

In 1942 *Wilson* (15) reported a case of myelopathy without anaemia, but examination of the bone marrow revealed changes of the granulopoiesis.

In a few but impressive papers, *Bastrup-Madsen* (1, 2, 3) has dealt with this problem. He has shown that instances of clinically patent multiple sclerosis should be classified as dysaemic myelopathy (due to deficiency of the antipernicious anaemia principle) in spite of normal conditions of the peripheral blood and the erythropoiesis of the bone marrow.

The granulopoiesis of the bone marrow, on the other hand, revealed definite signs of deficiency of the antipernicious anaemia factor in the nature of "pernicious anaemia neutrophils" (giant myelocytes, giant stab cells and macropolycytes).

Treatment with B₁₂ normalized the granulopoiesis of the bone marrow and in some cases the patient was cured.

A report of the following case may be instructive as to the above-mentioned clinical attempts at a differentiation of multiple sclerosis from dysaemic myelopathy.

In other words, we attempt to distinguish between two conditions having nearly identical clinical pictures.

As far as multiple sclerosis is concerned, we have for the present no treatment, while cases of dysaemic myelopathy may be successfully subjected to specific therapeutic measures.

CASE REPORT

Neurological Department, no. 16,573, man, aged 50 years.

History: No familial diseases.

Previously no complaints. For one year the patient had complained of vague subjective sensations of scintillations.

Four months later paraesthesiae in the fingers and the toes combined with increasing disturbances of the gait.

There was no speech disorders, or sphincter disturbances.

During hospitalization he was unable to walk.

Examination: No mental changes. Tongue normal. Cranial nerves: Normal conditions. Upper extremities: Normal conditions. Abdominal reflexes: diminished in the upper third and absent in the lower two thirds. Lower extremities: Knee

jerks "brisk" (spastic type). Ankle jerks absent. Plantar reflexes: No Babinski response; the Chaddock phenomenon questionably present. Position sense disordered. Severe ataxia. Gait: Ataxic with slight spastic disturbances.

The patient was unable to walk unaided.

Eye-examination: Visual acuity of right eye $\frac{6}{9}$; left eye $\frac{6}{18}$. Slight difficulty in circumduction movements of the eyes (oculogyric instability: *Viggo Jensen* (7, 8, 10). Ophthalmoscopy: Bilateral pallor of the optic discs. Visual field: Para-central and partial central scotomas on both sides for white and red.

Examinations: Achlorhydria after histamine test was demonstrated. Blood examination: normal. Bone marrow: normocytic erythropoiesis. The granulopoiesis revealed: giant stab cells and macropolycytes (unfortunately the patient had been treated with liver extract before admission to the neurological department. This obviously had diminished the original changes of the granulopoiesis of the bone marrow. Before this liver treatment the examinations of the blood were normal). The bone marrow was not examined before the liver treatment). Cerebrospinal fluid: Pressure normal. Cells 0/3. Protein 150 mg %, glucose 59 mg %. Adrenalin-liquor-saccharum-reaction: 1 0.008 % (diminished, indicating hypothalamic lesion, (*Munch-Petersen* (11)). Collargol reaction: medium nonspecific increase in protein content. Wassermann reaction: negative. Vibration test with Biothesiometer: Markedly decreased in the lower extremities. Flicker fusion test: Marked diminution spontaneously. No further decrease after administration of "narcodorm" intravenously.

Treatment: The patient was given intramuscular injections of liver extract with B₁₂ for a fortnight (Hepsol fortior Medicinalco). The same injections continued until now, twice a week. The patient was also given walking exercises.

On discharge he was able to walk unaided with one stick. The gait was still ataxic. The bone marrow was normal.

The haemoglobin percentage was raised from 80 to 88, and the number of erythrocytes was raised from 3.38 mill. to 4.4 mill. The colour index of the blood had decreased from 1.18 til 1.09.

The patient was readmitted six months later for follow-up.

The condition had gradually improved. The paraesthesia had disappeared. No symptoms from the eyes. During the last three months the gait had become almost normal. Examination of the cranial nerves: Normal. Upper extremities: Normal conditions. Abdominal reflexes normal. Lower extremities: No loss of power. The knee jerks and the ankle jerks are "brisk" (i.e. the ankle jerk had reappeared). Position sense in the toes slightly diminished. The vibration sense slightly reduced. Plantar reflexes normal. The Chaddock phenomenon questionable. The knee-heel-test showed medium ataxia. Gait: Almost normal, slightly ataxic. Slight hypaesthesia of the abdomen, gradually disappearing. Laboratory findings: blood normal. Bone marrow normal, especially normal granulopoiesis. Eye examination: Visual acuity: Right eye $\frac{6}{9}$; left eye $\frac{6}{6}$. Movements of the eyes normal. No instability of circumduction movements of the eyes. Ophthalmoscopy: Optic discs revealed questionable pallor. Visual field: Normal. No scotomas.

This case was at first taken to be one of sclerosis of the ataxic type.

The atrophy of the optic discs, in particular, and the scotomas would seem to justify the making of this diagnosis.

1 A-L-S-R = Suprarenine—cerebrospinal fluid—sugar—test.

The histamine- fast achlorhydria, however,—even if the patient was 49 years old—suggested an underlying dysaemic myelopathy.

In spite of the normal findings in the blood and of the normal erythropoiesis of the bone marrow, granulopoiesis of the bone marrow was abnormal, showing changes characteristic of pernicious anaemia.

During treatment with liver and B-vitamin B₁₂ the symptoms almost disappeared.

The patient recovered gradually without intermissions, and until now there has been no recurrence.

Changes of the optic discs with scotomas are no rare occurrence in subacute combined degeneration due to pernicious anaemia.

According to *Russel Brain* (5) such changes are found in 5 per cent. of such cases.

Recently *Benham* (4) has recorded visual field defects in subacute combined degeneration with optic atrophy. Liver therapy improved the condition.

Generally speaking, the “flirtation” between the spinal cord and the optic nerves is no recent clinical observation (cf. tabes dorsalis, multiple sclerosis, including Devic’s disease, etc.).

Finally, it would seem appropriate to say a few words about the problems of dysaemic myelopathy, in particular about the diagnosis and the therapeutic measures to be taken.

In 1934 the clinical entity of funicular infectious encephalomyelitis was proposed by the present writer (12).

The possible combined action of infection, of *funiculäre anlage* and of blood dyscrasia was discussed.

Probably some of the cases reported would, at the present time, be classed as myelopathy of the dysaemic type.

The case reported in this paper revealed an abnormal adrenalin-liquor-saccharum-reaction, indicating an abnormal function of the hypothalamus. This was also the case in a series of the cases reported in 1931, that were classed as funicular infectious encephalomyelitis. It was suggested at that time that in these cases the aethiological factor was a *forme basse* of epidemic encephalitis (*Economo*).

It has been suggested, also, that some abnormal condition of blood might depend on a dysfunction of the hypothalamic region. (*Müller* (13), *Wyburn-Mason* (16)).

This is the reason why we have to consider the possibility that dysaemic myelopathy, due to atypical pernicious anaemia, may, at

least partially, develop on the basis of a disordered function of the hypothalamus.

Another possibility to be taken into consideration is that encephalitis may be responsible for any such dysfunction.

The theory that for the present seems to gain ground is that of foci developing on the basis of allergic reactions. At least this hypothesis would now seem to be preferred to that of thrombotic occlusion.

But the modern trends as to the aetiology would seem to admit of more than one agent as being able to bring about the formation of the plaques.

Recently *Furtado* (6) has emphasized that many cases of funicular myelopathy, which to a varying extent resemble multiple sclerosis, are due to different aetiological agents, including dysaemic conditions.

In the opinion of *Furtado* the various types of funicular myelosis depend on abnormalities in the protein metabolism.

It is not, of course, feasible to decide in each case whether the myelopathy is due to multiple sclerosis in the usual sense of the term or to changes in the spinal cord of unknown aetiology.

But in cases where achlorhydria after histamine test is found and where the clinical examination reveals signs of combined degeneration of the spinal cord, treatment with vitamin B₁₂ should be attempted.

Jewsbury (9) has treated such cases favourably.

Weaver and *Neill* (14) have reported a case of subacute combined degeneration of the cord, which occurred without any evident pernicious anaemia in the peripheral blood and bone marrow. Meanwhile they found in this case excretion of abnormal amino-acids in the urine.

This phenomenon is seen in patients with untreated pernicious anaemia.

Consequently, vitamin B₁₂ was administered; evident improvement of the condition was observed and the abnormal amino-acids disappeared in the urine.

In the introduction to this paper the problems of the clinical and the histological diagnosis of multiple sclerosis was touched upon.

It was said that neither at the clinical examination nor at the post-mortem histological examination it was possible to secure a complete nosological entity.

Even in the case of clinical and histological conformity a nosographic entity only can be established.

Our knowledge of the aetiological factors is so far insufficient.

The final decision of the aetiological problem of the myelopathy must in each case depend on the result of a specific treatment.

Cases that for the present are classed routinely as multiple sclerosis may be highly different in origin.

As has been shown in this paper, the causal lesion may be a dysaemic condition of the pernicious anaemic type, perhaps atypical, manifesting itself in a dysaemic myelopathy, which, in turn, may be subjected favourably to "causal" treatment.

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CORTICAL CYTOARCHITECTONICS AND RELATED PROBLEMS. A SURVEY

By

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After the publication of a number of cytoarchitectonic works at the beginning of this century (*Brodmann* (12), *Campbell* (13), *Flechsig* (21)) the interest in this field was slight for a long period. In the current textbooks *Brodmann's* classification of areas was pictured without criticism, and his terms of areas are still used almost everywhere. It must, indeed, be admitted that they are quite practical amongst other things because the boundaries between the various areas are distinct, and because the sizes, and hence the number, of the areas are suitable if e.g. corticocortical connexions, an extirpated field, etc., are to be indicated. Still, the cytoarchitectonic works of recent years have shown that these distinct boundaries between areas hardly exist in reality. It may be mentioned here as a matter of curiosity that *Brodmann* never published the material on which his classification of areas was based!—However, the *Vogts* and their pupils continued working at the division of the cortex, until finally a division into about 200 areas in one hemisphere was reached! No material criticism of this development was voiced until 1946 when *Lashley & Clark* (31) passed under review the criteria which had hitherto been made the basis of the description of the cytoarchitectonic areas. Many of these criteria, e.g. the thickness of the layers, the arrangement of the cells, their form and size, density of cells, etc., are undoubtedly influenced by the folding of the cortex, the distribution of the vessels, and similar conditions, just as individual differences are considerable (*Kononova* (29)). The most important factor, however, is that this minute classification of areas does not seem to bear any relation to the function of the cortex; as a matter of fact, a holistic view is adopted to an increasing degree.

This criticism of "classical" cytoarchitectonics met with general approval, and amongst other things led to *Bailey* and *v. Bonin* publish-

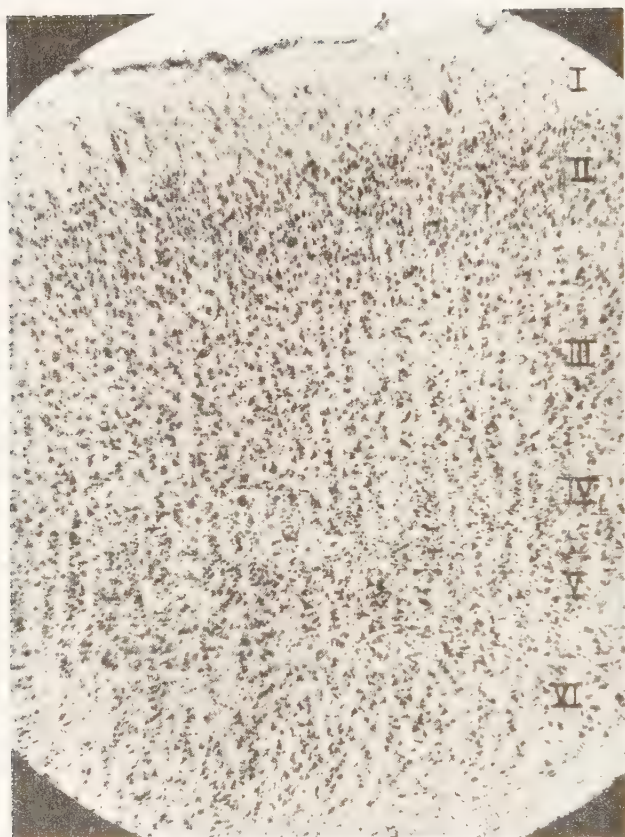


Fig. 1.

ing an important work on the isocortex of man (2). The material consisted of one hemisphere only, which in return was fixed immediately postmortem by perfusion of the arterial system. The brain was divided into 21 blocks which were cut serially, the sections being stained with thionin. The description was based on the following types: the "typical" 6-layered cortex was termed culminate (Fig. 1); beside this are grouped on the one hand the agranular cortex, on the other the koniocortex. The agranular cortex (Fig. 2) is characterized by being poor in granular cells, which have been replaced by small pyramidal cells, while the koniocortex (Fig. 3) has a well-developed interior granular layer and relatively small cells. Besides these three main types there are transitional zones, limitrophic variants. Bordering on the koniocortex there is thus a zone with relatively large cells deep in the III layer, the parakoniocortex. Around the allocortex the structure of the cortex is characteristic by the fact that the cells in the II layer increase

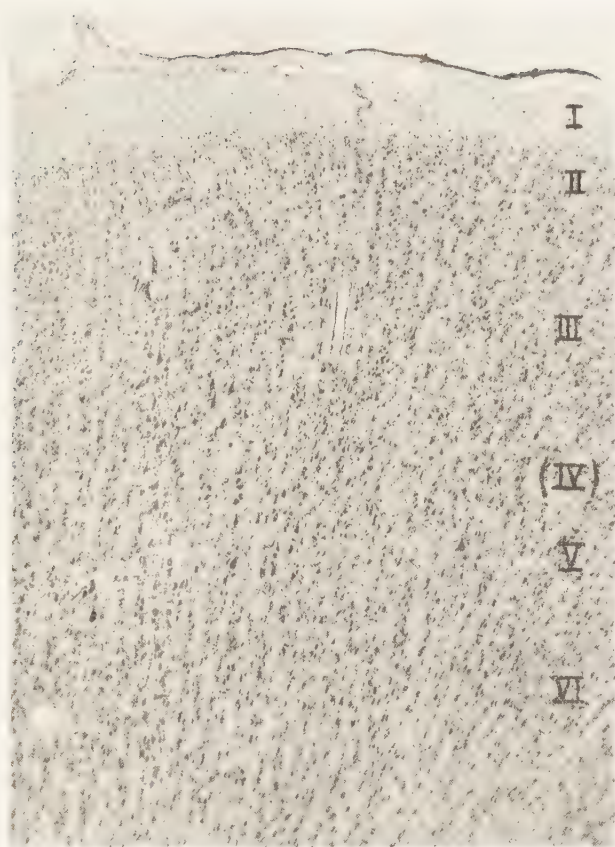


Fig. 2.

in size, and there is a tendency towards the formation of "glomerules" there. This is characteristic of the juxtallocortical variant. Finally there is, transitionally between agranular and culminate cortex, a zone in which the IV layer is but sparsely developed, dysgranular cortex.

On the basis of this comparatively simple system the whole hemisphere is described, it being divided into some twenty regions. Most of these are well-known, e.g. the precentral agranular region, the post-central koniocortex, etc. The new feature is the fact that large areas in the frontal, parietal, and temporal region are of so uniform a structure that, indeed, it is possible to describe differences in small areas, but these differences are so small that they do not exceed the changes that may be found in two adjacent sections, i.e. that large areas of the isocortex are of a remarkably homogeneous structure. This is contrary to the findings of previous workers; but after a thorough discussion of these works *Bailey & v. Bonin* write: "As one reads through their prolix



Fig. 3.

descriptions, and has the misfortune to remember what he has read, one is either repeatedly shocked by contradictions or suffers from what the French psychiatrists call *le phénomène du déjà-vu*."

There is no doubt that it is possible, on the basis of the ordinary cytoarchitectonic criteria, to divide the cortex into more areas than those indicated by *Bailey & v. Bonin* (as also stated by these authors); but the question is whether it would serve any reasonable purpose as long as our knowledge of a possible specific function of these areas is no more comprehensive than it is. *Kornmüller* (30) in 1937 found that in the rabbit there was a connexion between the type of electroencephalographic curve and the cytoarchitectonic areas, but later workers have not confirmed these findings, thus *Garvin & Amador* (23) in Rhesus monkeys found significantly deviating curves only in the precentral and postcentral convolution and in the occipital lobe, the curves even being identical in the former two places.

Le Gros Clark (15) thinks that when so many previous workers have agreed on the occurrence of certain general features in the classification of areas there must be a certain basis of it. The transition between areas is generally smooth, but in several places it is rather well-defined. This is also maintained by *Brodal* (8), who is of opinion that other staining methods must be used than the Nissl stainings. When the afferent fibres conveying impulses to an area are degenerated, extremely well-defined boundaries are especially seen with silver impregnation. But if the boundary between two cortex areas as regards the supply with afferent fibres is well-defined, this need not mean that the two areas cannot be uniform as regards the functions which are not directly dependent on the afferent connexions, as they may also be found to be morphologically of the same type.

In this connexion it should be noted that when the works of previous workers have often been so severely criticized as regards their indication of well-defined boundaries between areas, this is in part due to the fact that the maps published have for the sake of lucidity been provided with linear boundaries while in the text it has often been stated that actually there are transitional zones.

Previous workers' objectivity as regards the classification of areas of the cortex has in recent years been called in question from many quarters. This is, however, hardly justifiable, -for the following reasons: if a number of sections from a cortex are presented without paying special regard to the question how the sections are made in relation to the longitudinal axis of the gyri, it will be possible in the same preparation—at any rate in many cases - to point out differences in neighbouring areas which according to the ordinary cytoarchitectonic criteria justify a distinction between several areas. If, on the other hand, the sections are made at right angles to the surface and the longitudinal axis of the gyri, we shall often, in return, find remarkably homogeneous conditions as regards thickness of layers, density of cells, etc., in areas which by the former method of preparation it would seem possible to differentiate into several areas. Because of the sinuous course of the gyri it will be difficult to meet the above-mentioned requirements to the making of the sections unless a very large number of blocks are made the breadth of which correspond to that of the gyri. This has been done by i.a. *v. Economo*, but on the other hand clearness is often lost, as it will be necessary constantly to change preparations at the examination. *Bailey & v. Bonin* (2), as stated above, have cut up a hemisphere into 21 blocks, after careful arrangement as regards the direction of the section. The present author has

used about 30 blocks, which seems to give an expedient relation between the area of section and the consideration to the axis of the gyrus.

The folding of the cortex is also of great importance at the determination of areas (*Bok* (4)). At the curvature of the cortex, volume and arrangement of cells and layers remain constant. This involves that the form of cells and thickness of layers must be changed; but this will hardly cause any change in the function, which, amongst other things, appears from the fact that in the cases in which the boundary between two areas is well-defined, e.g. in the case of the area striata, this boundary is found in different places of the gyrus in the various brains. However, there is no doubt that ignorance of these conditions have given rise to mistakes at the previous classification of areas.

If the conditions mentioned above are considered together, it is easily seen that it is extremely risky to divide the cortex into many small areas if we exclusively apply the usual cytoarchitectonic criteria. It is, however, the criteria that should be criticized rather than the workers which have used them, apart from the fact that of course it would have been desirable that these workers had emphasized that subjectivity enters into the cytoarchitectonic criteria to a higher degree than is expedient. It is doubtful whether it is possible to use them at all in their present form. These criteria will not be discussed in detail here, but it may be mentioned that it applies to nearly all of them that the use of them has forced the observer to make a subjective evaluation (of the density of cells, the boundary between the layers at the measurement of the thickness of layers, etc.) which highly complicates a comparison between different investigators' works. The fact that every student of cytoarchitectonics ever since *Brodmann's* time has started with advance knowledge of *Brodmann's* classification, has undoubtedly played a role at the evaluation of the boundary of areas, etc. *Economo & Koskinas* (20), it is true, in 1925 tried to count cells, measure thickness of layer, etc., but as has been pointed out by i.a. *Agduhr* (1) their counting technique may be criticized on essential points; thus their total numbers of cells in the cortex (10^{10}) should be reduced materially, as differences in the size of cells have not been considered. *v. Bonin* (5) introduced new statistical methods for the determination of the size of cells (volume of nucleus) and compared the results from the various areas (6) in different species of animals in an attempt at finding a method to decide on a possible homology (although unsuccessfully). *Lashly & Clark* (31) used a planimeter for the determination of the area of the cells, and a counting chamber for the determination of the density of cells. Such methods are very time-wasting, but seem to me inevitable if an objective basis of cytoarchitectonics is wanted.

As regards future studies it is probable that it will be fruitful to correlate biochemical (histochemical) studies of the cortex with the results of cytoarchitectonics, amongst other things in order, if possible, to decide whether there is an agreement between the distribution of the cytoarchitectonic areas and the amount of various enzymes, proteins, minerals, etc., all over the cortex. In this way it may perhaps be decided whether there is any basis at all for continued purely cytoarchitectonic studies according to the criteria previously used, a question which has become of immediate importance after the publication of *Bailey & v. Bonin's* work (even though of course neurophysiological results must also be taken into consideration at this evaluation).

However, the classical histological methods have also proved to be of great value at investigations into the structure of the cortex. *L. de No* (35, 36) thus, mainly by means of the Golgi method, has attained to another picture—with its ensuing functional consequences. His theory on the vertically orientated functional units is well-known. As to the functional importance of the ordinary stratification, there are, however, certain elementary facts which presumably may be considered as established. The areas which receive specific thalamic afferent fibres are of the koniose type. The fibres terminate in the IV layer, while some other afferent fibres terminate in the II layer. A large number of the fibres of the pyramidal tract issue, from the gyrus praecentralis, which consists of agranular cortex—almost without layers II and IV, but with well-developed layers III and V. Here especially the V layer should contain the trophic centres of the efferent fibres. This fairly simple system is, however, far from applying in detail; conditions are undoubtedly more complicated; but our anatomic knowledge does not go any further. The alpha activity arises in the cortex layers collectively, and other methods have not been able to reveal the functions of the individual layers.

Thanks to modern neurophysiological methods our knowledge of the function of the cortex has during these decades increased so considerably that our knowledge of the structure of the cortex actually lags behind the functional insight, which perhaps to a certain degree may be due to the fact that many workers, neurophysiologists as well as neuroanatomists, accepted the minute classification of areas of the German School without reacting to the gradually very far-going subdivision of the Brodmann areas. Even in recent years, after the works of *Lashley & Clark* (31), *Liddell & Phillips* (33, 34), and *Bailey & v. Bonin* (2) have been published, there are neurophysiologists who support the "mosaic theory" (22). *Walshe* (48, 49) discusses these problems and stresses the necessity of using the principle of comple-

mentarity at the evaluation of electro-stimulation of the cortex, a field in which *Penfield et al.* (37, 38, 39, 40) have performed a number of valuable works. The brain maps prepared by these workers in *Walshe's* opinion only indicate something about the facts under the given conditions, with the technique used, but are hardly expressive of conditions *in vivo*. The problem is of great importance; as a matter of fact, says *Walshe*, it is necessary completely to review our interpretation of all stimulation experiments which have hitherto been made. *Liddell & Phillips* (33, 34) amongst other things have shown that changes in type and strength of current are of decisive importance for the effect of stimulation, and the narcosis used, the acid-base equilibrium of the animals, and other conditions are also of importance.

As another example of the fact that we should presumably appraise certain neurophysiological results with greater reserve than has previously been done, the fate of the suppressor zone may be mentioned. *Hines* (26) and *Barenne & McCulloch* (19) amongst others investigated the function of these zones, and several theories on this problem were advanced. Also cytoarchitectonically the occurrence of areas with a specific structure was established, e.g. area 4s, which was characterized by especially large pyramidal cells in the III layer. In 1948 *Clark & Ward* (14), however, failed to demonstrate the presence of cortical suppressor zones when unanesthetized animals were used, and *Druckman* (16) in 1952 completely disposed of the concept. The history of these zones shows that cytoarchitectonics has previously been ready with "an area" whenever the physiologists thought that they had found a special function in an area of the cortex. Investigators still work according to the principles of *Vogt* (3, 44); but the inclination to draw conclusions from structure in this sense to functional conditions has been reduced considerably.

Le Gros Clark (15) has asked the obvious question whether the cytoarchitectonic zones are characterized by specific fibre connexions. This question may in part be answered in the affirmative as regards afferent connexions; the lateral geniculate body projects to the area striata, the medial geniculate body to the supratemporal plane, the ventral thalamic nuclei to the postcentral region, etc. It cannot be expected, of course, that these afferent fibres in so complicated a structure as the cortex should exclusively terminate in accordance with the cortex fields of *Bailey & v. Bonin* (which, indeed, are vaguely defined). This is not the case, either; in most cases there is rather a considerable overlapping, but it is beyond doubt that there is a characteristic distribution of the fibres. If, on the other hand, we examine con-

ditions of the smaller areas of Brodmann or Vogt, it will only in a minority of cases be possible to demonstrate the presence of special afferent fibres extending to each area.

As regards the efferent fibre connexions, conditions are more complicated. While it has until recently been assumed that the source of the pyramidal tract was constituted by the precentral region, in the case of a few fibres also the postcentral region and the basal ganglia, recent investigations have changed our view of these facts.

After *Lassek's* (32) classical demonstration of the fact that only 2-3 per cent. of the descending fibres in the pyramidal tracts issue from the giant cells of Betz, *Brodal* (9, 10, 11, 45) has made important contributions. This author has now shown that also the temporal and occipital lobes have descending fibres in the corticospinal tract. These fibres extend in all the four corticospinal tracts and, like the great contingent of fibres from the motor areas, terminate in the internuncial cells in the medulla (and not direct in the large motor cells of the anterior horn as previously assumed). Furthermore *Brodal* (10, 11) has shown that there are also ascending fibres in the pyramidal tracts. These fibres constitute 2-3 per cent. of all fibres in the pyramidal tracts, are of varying diameter, have their course in all the four corticospinal tracts, probably terminate diffusely all over the cortex, and are chiefly crossed. Most of them issue from the forelimbs and more fibres come from the skin than from the muscles. Like the descending ones, these fibres have collaterals to a number of subcortical nuclei, amongst others the putamen, thalamus, substantia nigra, and pons. Actually the homogeneity of the organization of the ascending and descending fibre systems in the pyramidal tract is so pronounced that it seems justifiable to assume that they also functionally constitute one system. And as the descending fibres issue from the greater part of the isocortex, just as the ascending fibres terminate in large areas there, this means that at any rate cell groups in extensive areas of the cortex are functioning simultaneously at the execution of skilled movements. It is elementary knowledge that the afferent fibres are of great importance for the execution of coordinated movements, and it is probable that the ascending fibres of the pyramidal tract are of special importance for skilled movements; for it proves (*Brodal & Jansen*) that this fibre system gives off collaterals to the pons, which passes the impulses on to the cerebellar hemispheres, which are known in advance to be of importance for skilled movements. It must therefore be supposed that the enormously complicated system of fibre connexions necessary for the execution of skilled movements amongst others consists of the

ascending fibres of the pyramidal tract, the cerebellar tracts mentioned, numerous intracortical association connexions, and undoubtedly many others as well.

As mentioned above, *Brodmann's* classification of the cortical areas is rather practical. But as the anatomical basis is very uncertain, it has in recent years been attempted to provide a more objective basis of a classification of the cortical areas. As the function of the cortex is equally dependent on its connexions and on its internal structure, *v. Bonin* (7) has proposed making the above-mentioned distribution of the afferent fibres the basis of a classification of sectors which should include a frontal, central, parietotemporal, occipital, supratemporal, and a limbic sector, each of them corresponding to a thalamic nucleus. Perhaps a temporal and a perirhinal sector should be added. The concentration of the afferent fibres from the corresponding thalamic nucleus is not the same in the whole sector; but there is at any rate a well-defined anatomical background to such a classification, even though of course it may be objected that a concurrent cause ought to be attributed to the two other factors entering in the totality of the cortex, the internal structure and the efferent connexions. With our present knowledge it is not, however, possible to coordinate these three factors; therefore we must for the present operate with several different classifications which may be used according to requirement. In future the interareal connexions perhaps will prove valuable as the basis of a functionally useful classification, but our knowledge of these tracts is still too poor for such a classification to be proposed. Other conditions in the cortex as well, such as the contents of enzymes in the cells, the state of activity of the cells, and the like, may perhaps, as suggested above, be used as basis of the division. The electro-stimulation experiments (10) and physiological neuronography (17), as mentioned above, amongst other things because of dependence of external circumstances (narcosis, etc.) have produced results which it has so far been difficult to correlate with our other knowledge, but which of course will enter as valuable contributions to a future synthesis of our aggregate knowledge of the cortex and to a formulation of a theory of its function.

There has been no want of theories of this kind; but it has always been difficult to explain a number of elementary conditions characteristic of the function of the brain, the power of synthesis, of remembering, etc., when it was assumed that the impulses only arrived at the cortex and were transformed there, in order afterwards to give rise to the formation of an "efferent pattern", expedient in the given situation. The intermediate link has always been the difficult problem, *Pitts* &

McCulloch (41) have now tried to solve this problem by assuming that the unspecific afferent fibres activate the cells in the IV layer by turns, after which the impulses spread over the cortex like a wave with a certain frequency. The mechanism is compared with the scanning mechanism of television. The organization of the intracortical fibre systems are of decisive importance in this connexion. *Pitts & McCulloch* amongst other things use our cytoarchitectonic knowledge as their basis, but a much wider knowledge of these matters is required before the structural basis of theories of this type can be said to be all right, just as the proof that the postulated reverberating circuits actually exists has not been furnished.

Thus the question may be asked: if each cell in the cortex at the emission of the impulse emitted a flash, should we then see an accidental display of fireworks (like phosphorescence), or would there be a system, a pattern which constantly recurred, or would constantly changing patterns appear? Electroencephalography presumably only gives part of the answer to this question; still, the alpha rhythm is perhaps a very simple pattern arising as a sum of innumerable single impulses from cells which are in the same rhythm. It has been supposed that it is a question of definite systems of neurons in the cortex whose only, or main, task was that of maintaining a certain "central excitatory state" which was just reflected in the alpha rhythm. So far this is only speculation. On the other hand it is remarkable that the alpha rhythm may be registered in the areas which have an eulaminate cortex, but is missing in the agranular regions (*Jasper & Penfield* (28)). Perhaps the alpha rhythm may be interpreted as expressive of the above-mentioned scanning mechanism (*Walter* (50)), but conclusive experimental data are missing.

Thus it is possible that the great eulaminate areas should be interpreted as functionally "plastic" in the sense that the individual cells are "multipotent", i.e. that they may perform now one, now another function, dependent on the immediate requirements. Still, a "relative localization" presumably asserts itself so that the cells in one area of the cortex mainly performs one definite function, but if occasion should arise may enter into other functional patterns. Such a view is advocated by, amongst others, *Reinhold* (43) and *Goody & McKissock* (25). This hypothesis is intermediate between the mosaic theory proper, including the Vogtian theory of pathocclisis, and the holistic view of the function of the cortex. It is not intended to discuss these problems in detail here, but by way of example it may be mentioned that the areas of the cortex which are especially involved in the formation of speech also contain neurons which contribute to the system of the

pyramidal tract, just as at any rate certain elements of the function of memory are represented there. In the parietotemporal sector a number of functional patterns are also present. Everything tends to show that the concepts of localization, centre, etc., should be taken up for review. In 1941 *Jansen* (27) wrote, "One suspects that the problem of localization in the case of the cerebral cortex perhaps is not a question of an either—or, but rather of a both—and, i.e. a combination of localized elementary functions on the one hand, and a general function on the other, conditioned by an intimate interplay between the cortical areas and between these and the subcortical centres." Our knowledge of details concerning the cortex has been increased considerably since then, but our view of the function of the cortex as a whole has not been changed materially.

The concept of localization itself within neurology at any rate includes anatomical localization, clinic-pathological localization, and functional localization. The last-mentioned localization has especially been used in a varying meaning by the different authors, and confusion is great in this field. The same applies to the concept of "functional organization", this catchword which is encountered in almost every work on the cortex. On the whole semantic problems often crop up at the treatment of these questions. *Bailey & v. Bonin* define "functional organization" as "the spatial distribution of nervous processes in the cortex. To show how and to what extent the structure of the cortex determines its "functional organization" . . . must be our aim. We are far from having achieved it." This is, indeed, sadly true, but there is hardly any doubt that among the methods which, besides the neurophysiological ones, may carry us further, the quantitative histochemical methods are of great importance, just as *Glee's* silver staining technique has already yielded very promising results. In their mention of the investigations into the fibre connexions of the cortex *Bailey & v. Bonin* write, "This is not a glamorous task; no oscilloscope flashes, no Geiger counter clicks . . ." This also applies to the above-mentioned histochemical methods, but the importance of the results reached in this way is not less than that of those reached by more "dramatic" methods.

SUMMARY

A survey is taken of recent cytoarchitectonic works; especially that of *Bailey & v. Bonin* is discussed. It is pointed out that the cytoarchitectonic criteria undoubtedly should be revised, as the influence of the cortex folding on the distribution and form of the cells, etc., has not

previously been sufficiently considered. Quantitative methods must be used, although they are very time-wasting, and the results of quantitative histochemical investigations of the cortex as regards enzymes, minerals, proteins, etc., be compared with the brain maps now accepted. In this way it may perhaps be decided whether the functional importance of these anatomic brain maps is greater or less than has hitherto been assumed.

The afferent and efferent connexions of the cortex are mentioned, and on this background the problem of the classification of the areas of the cortex is discussed. It is concluded that for the present we must operate with several different classifications as our total knowledge does not yet permit any unity classification. The sector classification of *v. Bonin* based upon the distribution of the afferent fibres from the various thalamic nuclei is mentioned. Finally an account of some recent theories on the function of the cortex is given, and on the background of this the great need for detailed knowledge of the microstructure of the cortex is emphasized.

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SØREN KIERKEGAARD IN AMERICAN PSYCHOLOGY

By

ERIK SKINHØJ and KIRSTEN SKINHØJ

If present-day American university men were asked the following question "Who is Søren Kierkegaard?", we guess that the great majority of answers would be that he was a famous psychologist, perhaps even with the addition "of the Freudian school". A reader from Søren Kierkegaard's mother country will undoubtedly be a little surprised the first time he encounters our old philosopher in the ranks of famous psycho-analysts, as for instance in the following quotation from Rolly May, "The Meaning of Anxiety", p. 210: "The description of this state of conflict ranges from . . . to the systematic endeavors of Freud, Kierkegaard, Horney and Fromm to discover the nature of this conflict".

This example is not unique, and in the American psychological literature, which like a breaker has washed over the old world during the past 10 years, we find quotations from Kierkegaard and references to Kierkegaard over and over again, not only in the inevitable historical introductory chapters of such publications but also, and to an equally high degree, in topical sections of discussion in which Kierkegaard's viewpoints and formulations are accepted or contested in a way which does not convey the impression to the less knowing reader that it is now one hundred years since Kierkegaard would have had the possibility of making a retort.

It therefore seems to us that somehow it is a duty to examine from Danish quarters the causes and justification of this new trend in Kierkegaard's constantly increasing international fame.

This is the sole purpose of this article; thus we have not intended to add another contribution to the practically endless studies on Søren Kierkegaard's thoughts and life.

The task we have set ourselves is simplified considerably by the fact that practically all references to Kierkegaard in the mentioned

literature date from only one publication: Walter Lowrie's translation of "Begrebet Angst", published under the title of "The Concept of Dread"; it appeared in 1944—i.e. exactly one hundred years after the original edition was brought out.

„Begrebet Angst" has also tempted certain Danish Kierkegaard investigators (Ostenfeld, Kjer Petersen): on the basis of its dogmatic-religious charter, its ambivalent hatred of Hegel and its theological-philosophical style they have attempted to extract the underlying psychological observations and theories. Such attempts have been sharply, even contemptuously, criticized by many other authors (see Aage Kapell: "Kierkegaardstudiet i Norden"), and the discussion of the fundamental justification of this method will presumably never be brought to an end, but whether it is justifiable or not, it is nevertheless from such one-sided abstraction, in fact from quite a few sentences, detached from their context, that the whole of this part of Kierkegaard's American fame has been created.

Things like these must be considered in order to understand the following statement by Mowrer: "Freud's theories are necessary conditions for understanding Kierkegaard's psychological production" . . . a mouthful which a classic Kierkegaard admirer finds it hard to swallow. Let us now consider what exactly it is in Kierkegaard's concept of anxiety which has actually anticipated psychology for almost one hundred years.

Here we must undoubtedly first of all consider the sinister present-day actuality of this concept. The whole of our civilization is in the sign of anxiety. It imbues everything, either as pure, undisguised anxiety or as a forced, convulsive escape from anxiety. We need only mention at random such concepts as inflation, crisis, cold war, existentialism, abstract art, the deterioration of jazz, Jehova's witnesses, the increasing number of neuroses, the rise in the number of suicides etc., etc. No wonder then that anxiety comes to take up quite a fundamental position in present-day psychology and sociology.

But the actuality alone does not explain the interest in Kierkegaard's concept of anxiety, for numerous authors have been absorbed in these subjects both before and after and have remained in oblivion.

In his book "Begrebet Angst" Kierkegaard said, "The concept of anxiety is hardly ever dealt with in psychology, and I may therefore point out that it is entirely different from fear and similar concepts which relate to something definite . . .", and later, "Just as the relation of anxiety to its object, to something which is nothing . . .".

Kierkegaard was apparently here the first to draw sharply the distinction between the concepts of fear and anxiety which Freud later

made to an essential point in psychology—and with definitions corresponding exactly to those of Kierkegaard. Unfortunately, this has later been neglected to a considerable degree, especially in the field of experimental psychology, causing a severe confusion of ideas. This distinction is of special importance in the psycho-somatic medical research, as fear and anxiety may here exert diametrically opposite effects on the vegetative tonus, as has been shown, for instance, by Wolff in the case of the stomach secretion in man.

Not only by the separation of these concepts but also with regard to their dialectical coherence did Kierkegaard anticipate the most modern interpretations.

When, for instance, in the section on "Anxiety considered dialectically with reference to guilt", Kierkegaard says that as soon as the guilt has been established, the anxiety will be over, then this corresponds to an essential point in the demonstration by modern psychology of the fact that a materialized situation of danger represses the anxiety. Kierkegaard pointed out that exactly this manner of repressing anxiety creates a violent ambivalence with regard to guilt, and, similarly, psychology of today shows how anxiety may lead to an ambivalent craving for concrete dangerous situations, or for other materialization of the metaphysical anxiety, e.g. in the form of guilt and the punishment incidental thereto. Both in the concept of ambivalence and in the prominence given to the dynamic energy in the concept of anxiety we—and thus also Kierkegaard—have here approached something very essential in the modern interpretation of neuroses. Kierkegaard himself was apparently also fascinated by the universal and commonplace validity of these ideas, so that—quite outside the scope, form and style of his work—he made the following observation from everyday life: "The hypochondriac is frightened by every trifling event, but when the important events occur he begins to breathe again—and why? Because after all the important reality is not so dreadful as the possibility he himself had imagined and, so imagining, used all his strength, whereas now he can apply all his strength on reality".

In order not to create a false impression of identity between Kierkegaard's concept of anxiety and the view of anxiety as expressed by the dynamic psychology, it may be appropriate, before a further demonstration of points of resemblance, briefly to consider Kierkegaard's idea of anxiety.

Kierkegaard said, "Man is a synthesis of the psychic and the physical. But a synthesis is inconceivable if the two do not unite to form a third. This third component is the mind. Man in a state of innocence is not merely an animal, for were he ever in his life merely animal, he

would never become a human being. Thus the mind is present, though unconscious and dreaming. Provided then it is present, it is in a way a hostile power, since it constantly disturbs the relation between soul and body, which indeed is in existence but nevertheless is not, in so far as it only comes into existence by the aid of the mind. On the other hand, it is a friendly power which just aims at establishing the relation. What then is man's relationship to this ambiguous power, what is the position of the mind in relation to itself and its origin? It takes the form of anxiety"¹.

Later, Kierkegaard said, "In a logical system it is easy enough to say that the possible passes into the real. In reality it is not so easy, and an intermediate link is required. This intermediate link is anxiety".

And later again, "Anxiety is the possibility of freedom . . .".

In Kierkegaard's view, anxiety thus becomes something entirely fundamental, something that is inevitable in human development and ripening—and again in its dissolution, in "sin". when, according to Kierkegaard what happens is exactly that the synthesis between psyche and body is again loosened; this is illustrated, for instance, by the sexual urge where the physical component—the Freudian drive—becomes so strong that mind's synthesis is disrupted—and anxiety is created. A thing worth considering in greater detail is Kierkegaard's view that anxiety is created in the dialectical process between soul, body and mind, in an attempt at translating these concepts into a more modern nomenclature. "The body" corresponds exactly to "das Es" in the Freudian psychology, i.e. the instinct, the animal. "The soul" has certain, indeed actually the most essential of the attributes and functions of "das Ich" (intelligence as a tool with which to realize the desire from "das Es"), and "the mind" is contained in at least one of the most important functions of "das Ueberich", namely the ethical ideal-formation and its indisputable and uncompromising demands. But at the same time "mind" implies the harmonious synthesis which is actually foreign to the Freudian pessimistic psychology. Expressed in this way we see how Kierkegaard's anxiety becomes a product of disturbances in the dialectical harmony between das Es, das Ich and das Ueberich, and just for this reason it will manifest itself everywhere

¹ It should be noted here how Kierkegaard accepted his detested opponent Hegel's dialectical view of the fusion of contrasts into a reversible higher entirety and thus acquired a psycho-somatic view of oneness, towards which we have just of recent years begun to grope our way. It should also be noted in this connection that from this Hegelian view of psyche and soma via Marx's and Engels's elaboration of the dialectical materialism there is a direct line to present-day Soviet-Russian psychology.

when "the free will" forces the individual to make a decision, thus in every situation where choice or conflict is concerned. Later, in the comparison between Freud and Kierkegaard we shall revert to this problem.

Kierkegaard carried through his interpretation of anxiety with unique consistency. If we accept his premisses, we must also follow him when he says, "Therefore, anxiety will not be found in animals, for just because of their naturalness they are not under the influence of mind", and later, "That there are children in whom it is not present, proves nothing, since it is not found in animals either and, the less mind, the less anxiety". Later again, Kierkegaard says in his most poignant style, „But if the speaker thinks that it is a great thing for him never to have experienced anxiety, I shall be glad to initiate him in my explanation that it is due to his being of a very shallow mind". (Even though Kierkegaard's premisses are here very far from those of modern psychology, it is still worth noting that certain misunderstandings with regard to the concept of anxiety have just arisen from an inadmissible identification of anxiety-like states in animals with human anxiety).

To Kierkegaard the only way to freedom, i.e. the highest stage of human civilization and the zenith of the individual mind, was just the way through anxiety. "Anxiety is the possibility of freedom". But this way is appalling, for, "No Grand Inquisitor has such terrible torments ready as anxiety, and no spy knows how to attack the suspect so ingeniously just at the moment when he is weakest, or knows how to tighten the snare in which he is to be caught, as anxiety knows it, and no shrewd judge knows to examine, indeed to examine, the defendant in the same manner as anxiety does, anxiety which will never release him, be it during diversion, in the noise of the day, at work, by day or by night".

Therefore, the way to freedom is possible only for the genius, indeed only for the religious genius. Others have to stop on their way, like the ancient Greeks whose anxiety was bound in the belief in fate, or Judaism where "the laws and the guilt" play the same role as did "fate" to the ancient Greeks. Such types of the human being, who undoubtedly in Kierkegaard's eyes constitute the great majority of mankind, are excused. Like the child, they possess a certain innocence and have no possibilities of getting further. But he who has not the right of childlike innocence to remain half will incur damnation unless he ventures to confront anxiety. To him, anxiety becomes "the demoniacal anxiety", "anxiety for the good", which he does know but from which he tries to escape. Escape is impossible though. He is unable to minimize the problem, for it appears whenever a choice has to be made.

and, "If it is dismissed because only a trifle is involved, then anxiety will render this trifle conspicuous just as the small town of Marengo became conspicuous in the history of Europe because the battle of Marengo was fought there". He must then remain in the demoniacal, in bondage, and this bondage ensnares his personality, deprives it of all its natural communications and causes him to take to "hypochondria and vagaries".

Many may perhaps wonder why a religious thinker as Kierkegaard did not leave any possibility of relieving anxiety through faith, but this would have been an utterly alien idea to Kierkegaard. The tree will give to the individual the full and whole responsibility, and only in the very last phase of freedom when all anxiety has been experienced without compromise God will come to his relief.

As mentioned in the introduction, the purpose of this paper is to compare this view of anxiety of Kierkegaard's with today's concept of anxiety, especially as it has been developed in America. However, as the latter is inextricably bound up with Freud's fundamental principles, it is necessary first to compare Kierkegaard's interpretation of anxiety with the Freudian view. Points of resemblance have already been mentioned: The key position of anxiety in all psychology, a dynamic according to Kierkegaard dialectical—interpretation of anxiety and its distinction from fear and similar concepts in that anxiety is metaphysical in the sense that, subjectively, it has no object. But in spite of these essential points of resemblance the differences are nevertheless greater. Whereas to Kierkegaard anxiety occurs whenever "the relationship between soul and body is disturbed", thus, as previously mentioned, in any conflict between *Es*, *Ich* and *Ueberich*, then anxiety according to Freud is exclusively the result of repressed "*Es*"-forces—originally even exclusively repressed sexual libido. It is true that Freud during his later years modified his view that repressed libido is automatically turned into anxiety by adding that the actual danger to which the individual would be exposed if the libido were not repressed also plays a part in the manifestation of anxiety. But the dynamic energy of anxiety was still in Freud's opinion the repressed libido. This means that where Freud notwithstanding all protests and interpretations from his orthodox devotees stuck in his biological and anticultural perception of the psyche, Kierkegaard actually anticipated a much less narrow and one-sided view with the germ of a modern psychology of sociological determination. But the truth is that it remained in germ, and these two *outré* individualists strangely came to grief each in his own way: Freud who to the last stubbornly maintained that *das Es* is the source of all gratification, whereas the function of *das Ueberich* is

joy-killing, and Kierkegaard who during his later years more and more obstinately asserted that good fortune could only be gained through the complete submission of the body, that is to say by the unconditional surrender of *das Es* to *das Ueberich*.

The perhaps most decisive difference between Kierkegaard's and Freud's concepts of anxiety should be viewed against this background, namely the phenomenon that while anxiety according to Freud becomes something negative, something that should be avoided or obviated, then anxiety in Kierkegaard's interpretation becomes a positive factor which can, indeed inevitably must, be utilized in the development.

In certain concrete applications, such as, for instance, in speaking of the connection between anxiety and sexual desire, Kierkegaard's introspective method cannot, however, give the same right to generalization as Freud's clinical experiences, and it is undoubtedly attributable to Kierkegaard's lack of experience when he maintains that anxiety arises through gratification of the sexual desire, while, as is known, Freud's view is the diametrically opposite. But nevertheless it is an open question whether Kierkegaard's formulation has not a greater practical validity than that of Freud in a civilized community with very strict sexual taboos—a view which on closer consideration, however, is Freud's rather than Kierkegaard's.

Broadly speaking, after Freud the development within the domain of research created by him has been characterized by an ever deepening dissociation from Freud's psychologic-philosophical ideology, though his working method and his fundamental views concerning the structure of personality and with regard to the somatic equivalents of mental energy have been maintained. It is interesting to see how this development has given rise, among other things, to such revisions of the Freudian perception of anxiety that it has in certain respects become increasingly like Kierkegaard's views.

This applies to the fundamental problem of the origin of anxiety which we have already dealt with earlier; there is now a distinct tendency to assume that anxiety is not only due to repressed libido, but that, in general, it is an intermediate product of every situation where a conflict is involved, and that moreover, as formulated by Mowrer, it "occurs most frequently where the problem is of an ethical nature".

This also applies to the essential features in the neurotic development resulting from the individual's reluctance to confront the anxiety. It is true that Kierkegaard here mentioned hypochondria, but he attached special importance to the disturbances in interhuman relations caused by such a process: "The demoniacal does not confine itself with something, but confines or locks up itself, and there is the profundity

of life, that constraint just makes itself a captive.—The constraint becomes more and more constrained and wants no communication. This can be observed in all spheres". Stressing this neurotic isolation, Kierkegaard places himself quite centrally in the sociology-minded psychology where the main problem just is that of interpersonal relations (Lynd, Horney, Fromm, Sullivan and others). It is moreover a feature common to all these authors that they emphasize anxiety as "the dynamic centre" (Horney) of development of interpersonal relations. In this connection, however, it must be pointed out that Kierkegaard only mastered Hegel's dialectics with imperfection, for while, to Sullivan, May, Tillisch etc., disturbances in interhuman relations are cause as well as effect in the formation of neuroses, they are to Kierkegaard just the effect of intrapsychic derailment. The materialization of, i.e. the object-formation for, the diffuse anxiety with a view to relief also represents viewpoints which have become highly topical today. Horney, like Kierkegaard, has shown that the anxiety subsides when "the guilt has been established", and Fromm, in his large work on the psychological conditions and contents of Nazism, has substantiated how fatalism may reduce anxiety by freeing the individual of responsibility. It is also Fromm who has most sharply drawn up this connection between freedom and anxiety, which Kierkegaard saw and formulated by saying, "Anxiety is the possibility of freedom".

However, what has more than anything else drawn Kierkegaard's name into today's discussion of the psychology of anxiety is apparently his demonstration of anxiety as a positive factor, a school for the development of personality. During recent years this viewpoint has led to great enthusiasm from widely different quarters, with or without any knowledge of Kierkegaard's publications.

Goldstein's studies on anxiety reactions and anxiety patterns in individuals with organic cerebral lesions are already classic; among other things Goldstein arrived at the view that a necessary condition of rehabilitation is that the individual confronts the anxiety instead of protecting himself against it through rigid imperative patterns.

According to R. May, H. Lidell summarizes in animal psychology the experiences concerning anxiety as follows: "The capacity to experience anxiety and the capacity to plan are two sides of the same coin". In his own publications, Lidell prefers the term "vigilance", but in this connection it is identical with Kierkegaard's "anxiety" and with "anxiety" as used in psychodynamics, as it stands for the complex of feelings implied in the question, "What happens next?", in contrast with fear's "What is it?", which is devoid of perspective.

In child psychology, Lauretta Bender, among others, emphasizes

the role played by anxiety in the development of personality, pointing out how a separation from mother— or mother substitute — at the age of 1 or 2 years may give rise to severe disturbances of behaviour and development, characterized by psychopathic features and the absence of anxiety.

Blatz's well-known theory of development: security with agent → insecurity → security without agent covers, though with the use of insecurity instead of anxiety, exactly the same conception of anxiety as a necessary and inevitable link in the process of ripening.

Based upon his own experiences in psycho-analytical practice Yaskin considers anxiety a sort of fever in the sense of the term that it signals a mobilization of the forces of the organism. Mowrer's formulations appear the most well-defined and those with the deepest practical perspective when, on the basis of his studies on the processes of learning and development, he declares to be in complete agreement just with Kierkegaard with regard to the latter's conception of the educative importance of anxiety. With a warning to psychologists and psychiatrists he adds that anxiety should not be considered a thing to be analysed, shocked or lobotomized away, but that, on the contrary, it is a state the potential energy of which we should learn to utilize in a positive direction.

In the introduction, we put the question of the causes and justification of the Kierkegaard fashion in modern psycho-analytically orientated literature. The first part of the question can be answered by stating that, one hundred years ago, Kierkegaard actually anticipated a number of the psychological observations and problems which take up a central position in the leading psychology of the present decade, and in a way this also implies the justification of the interest taken in his works today. On the other hand, the fact cannot be ignored that the similarity of viewpoints results in part from a total abstraction from the whole of the dogmatic system and the religious view of life which to Kierkegaard himself formed an indivisible whole. Only in this way will the apparent paradox become intelligible that the individualistic, reactionary and Uebermensch-minded metaphysician Kierkegaard is today appropriated by the most progressive and socially inclined part of American psychology. This paradox was apparently always Kierkegaard's fate. At the time about his death his most fanatical defenders in Denmark were liberalism and the budding labour movement, which ideologically and politically were most alien to him. In Germany, the fame of Kierkegaard the dogmatist was first and foremost created by antidogmatic scripture critics, such as, for instance, Schrempf and later Baumbach, and in

France the religious Kierkegaard has been popularized above all by a godless existentialism.

If we recognize—though conditionally—the justification of Kierkegaard's fame as a sort of pioneer for modern dynamic psychology, the question inevitable arises how it might come about that Kierkegaard a whole century prematurely could arrive at his psychological ideas and formulations. If the answer were that this was just due to his genius, this would only be redundant, for not even the genius creates out of nothing but must have certain necessary conditions. As far as we can see, these were chiefly two. First, that in spite of his dogmatic disposition he was able to regard religious history as a sublime mythological formulation of the wishes, dreams and problems of ordinary human beings, and thus he acquired ample compensation for his failing ability to get to know other people through personal intimate communication. The second, and undoubtedly the most important, condition is rooted in Kierkegaard's pathopsychology rather than in his genius, namely in the fact that his depressions gave him such a relentless, self-reflective and self-critical insight that in this manner he reached a form of auto-analysis which would not be bestowed on a normal individual.

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VACUOLIZED LYMPHOCYTES IN LIPOIDOSIS

By

H. P. STUBBE TEGLBJÆRG and CLAUS MUNK PLUM

The first history of juvenile amaurotic idiocy was reported by *Stengel*, who in 1826 in the Norwegian magazine *Eyr* described how all the four children in a family successively grew blind, imbecile, and epileptic, and died about twenty years old.

In 1881 retinitis pigmentosa was described by *Tay*, and in the following decades numerous and different syndromes of lipoidoses were registered under the well-known names: Morbus Hand-Schüller-Christian, Tay-Sachs, Spielmeyer-Vogt, Niemann-Pick, Gaucher, etc.

In neurological hand-books and journals steadily increasing numbers and varieties have appeared. Emphasis was laid sometimes upon the neurological, ophthalmological, or psychiatric symptoms, sometimes upon their hereditary character or their histological or biochemical problems.

In Scandinavia several important works about lipoidosis have appeared. Especially *Torsten Sjögren's* monography from 1931 must be mentioned. The author analyzes 115 cases and makes a comprehensive study of the hereditary problems indicating a monohybrid recessive succession.

Einar Sjövall in 1934 made a thorough analysis of the histological changes in the central-nervous system. He stresses the resemblance between these lipid changes and those found by *senium præcox*.

The histological findings in the Purkinje cells and of the macroglia in the cortex of cerebrum and cerebellum as well as in the neostriatal ganglia, agreed well with the clinical pyramidal and extrapyramidal symptoms.

Schob and *Sjövall* further demonstrated cells with vacuoles, "scum cells", due to lipid accumulation, in the reticular cells in the lymphatic glands and the spleen as symptoms of a general metabolic disturbance.

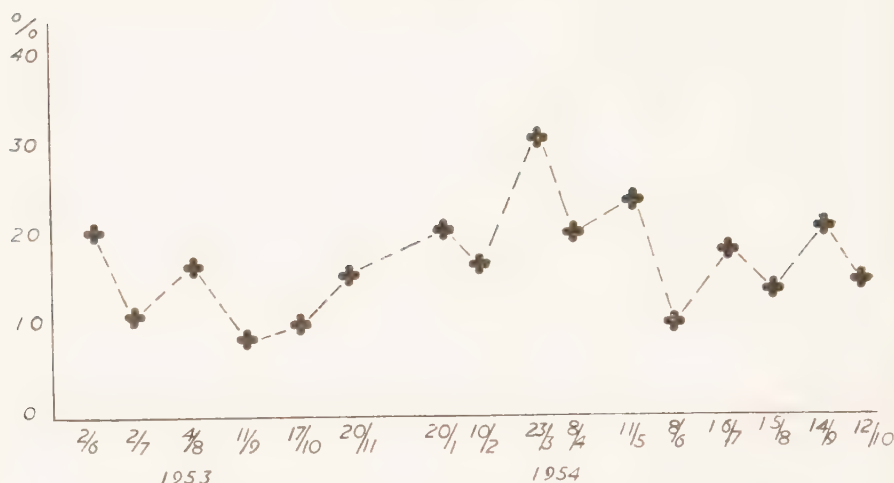


Fig. 1 showing the variation in numbers of vacuolized lymphocytes. Ordinate: percentage of vacuolized lymphocytes of total number of lymphocytes. Abscissa: time.

Von Bagh & Hortling in 1948 found vacuoles even in the stroma of the lymphocytes, and lately *Rayner* in 1952 found the same abnormal lymphocytes in the blood from relatives of patients with juvenile amaurotic idiocy. Otherwise these persons were apparently healthy.

This was confirmed quite recently by *Nissen* 1954, who found four Norwegian families with several cases of juvenile amaurotic idiocy. In the blood from all the patients, and from several of their normal relatives, lymphocytes with vacuoles were demonstrated.

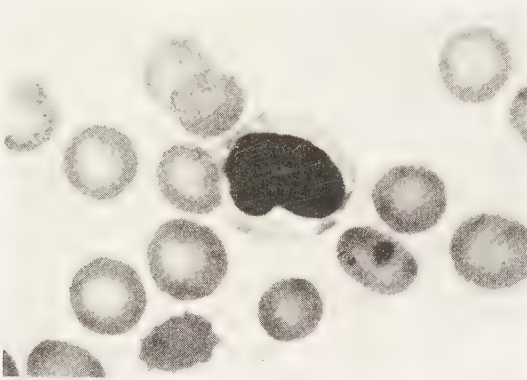
Nissen emphasizes that two of these families live in the same remote valleys where *Stengel* in 1826 found and described the disease which some eighty years later was named *Spielmeyer-Vogt's disease*.

In this preliminary report we shall try to elucidate some of the problems connected with the hereditary abiotrophic diseases which *Krabbe* in his book: *Nervous diseases and growth disturbances in childhood* called xanthomatoses or lipoidoses. Recently *Siive* in his hand-book of children's disease has named these abiotrophies reticulo-endothelioses.

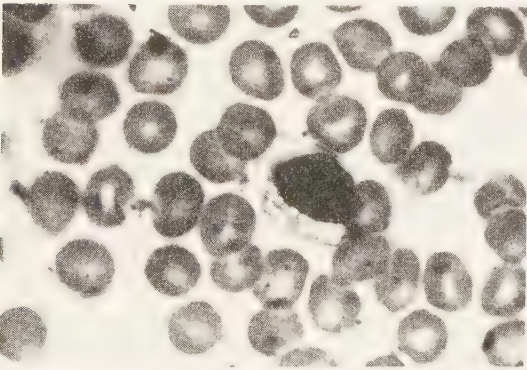
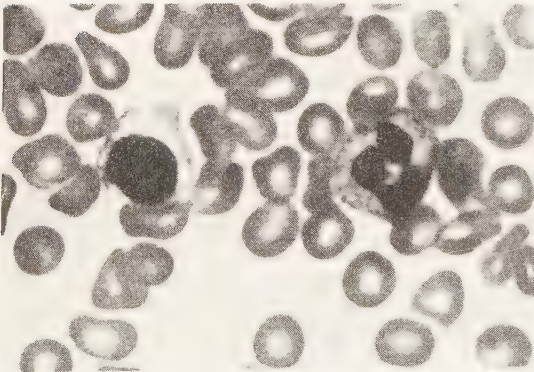
Our material consists of patients treated at the Departments for Epileptics in The Filadelfia Colony, Dianalund, and a few of their relatives, supplemented with a few cases submitted to us from the hospital for feeble-minded, Ebberodgard, and the Neurological Department of Rikshospitalet in Oslo.

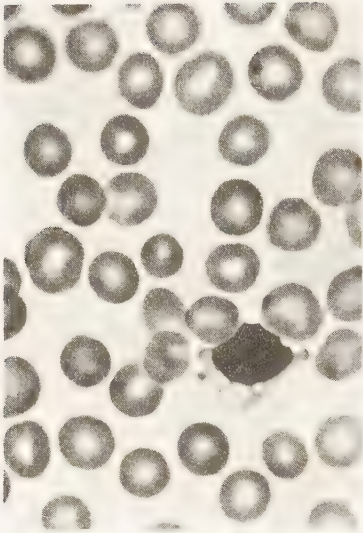
The neurohistological examinations were made by *K. A. Lorentzen*, M.D., at the Institute for Cerebral Pathology in Århus.

VACUOLIZED LYMPHOCYTES

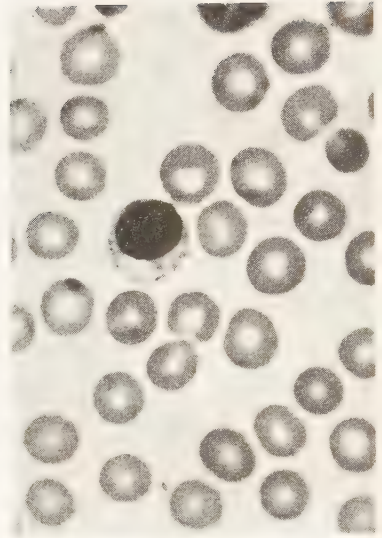
*Fig. 2 a.*

Blood-smear from the mother to Case 1 and 2.

*Fig. 2 b, Case 1.**Fig. 2 c, Case 2.*

*Fig. 2 d.*

Sister to Case 1 and 2, born 1945.

*Fig. 2 e.*

Sister to Case 1 and 2, born 1948.

Case No. 1.

Female born 27/6-38, Filadelfia J. 28.747.

Family history. Her mother's father died insane and his brother blind. The rest of her ancestry healthy. She is the first born of five. Number two is identical with case No. 2. Number three, a boy 11 years old, four and five, 9 and 6 years, all show "cherry spot" in the retinae, but no neurological or psychiatric abnormalities.

At birth she was asphyctic in medium degree, but she developed quite normally until she was six years old. Then her mood was altered. She grew restless and agile. At eight years old dementia and amblyopia set in. This increased, and at ten years old she was nearly blind with a psychosis showing schizophrenic traits. She was autistic, aggressive, suspicious, hallucinated with eating refusal, probably on account of her hallucinations. At twelve years old, nearly with her first catamenia, general epileptic convulsions started, four to six a year. Her vision vanished, so that only light-perception in the right half of the visual field remained. Admitted to Filadelfia 18/2-1952.

Objective findings: General spasticity, but mainly on the left side. Her tendon-reflexes on the extremities are all abolished.

Further details in the neurological examination could not be stated on account of her dementia. Ophthalmoscopy revealed typical pronounced retinitis pigmentosa.

During the last three months constantly confined to bed with steadily advancing emaciation. Contraction of both knees makes it impossible for her to stand alone or to walk. Her weight has diminished from 36 to 27 kilogrammes during these two years. Her psychiatric state is mostly complete apathetic; but now and then she shows maximum anxiety with screams, agitation, and uncleanness.

Laboratory-examination: Normal findings in the cerebrospinal fluid, urine, and

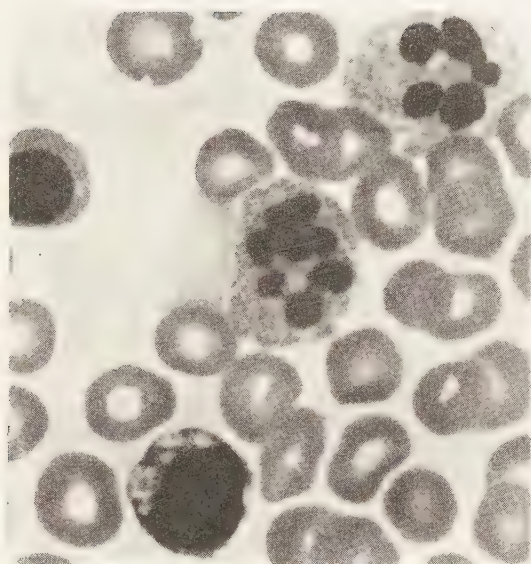


Fig. 2 f.

Brother to Case 1 and 2, born 1943.

blood apart from the free cholesterol. Only 13 per cent. of the total amount of cholesterol was found as free cholesterol (normally 20-36 per cent).

A differential count showed a great number of vacuolized lymphocytes. In fig. 1 the variation of the number of vacuolized lymphocytes is given for a period of 18 months; it will be seen that the number varies from 8 to 32 per cent.

Case No. 2.

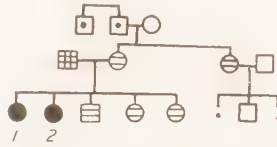
Female born 28/1-1942. Filadelfia J. 32.196.

Sister to Filadelfia J. 28.747 and the second of five. Her birth was normal, but her development a little retarded. She walked at eighteen months and talked at two years old. At four years old she was ill from scarlatina. Otherwise healthy and normal until she was nine years old. The two first years at school she made normal progress; but then her intelligence began to fail, and she was transferred to a school for children with difficulties in behaviour. Even here her training was poor. She was frightened, restless, and hallucinated, seeing "wolves and eyes on the ceiling."

At ten years old her appetite was morbidly increased and her weight strongly augmented. Her catamenias started at eleven years old. At twelve years old she was dim-sighted and now epileptic fits with general convulsions started, returning four to six times a year. During the next ten months her vision failed, so that she is now almost blind, especially the first days after her epileptic fits.

Her mental state during the last year has been very irregular. As a rule she is silent, quiet, and kind, playing as a three years child with her dolls. But at periods she is very unruly, screaming, aggressive, or sexually excited with unveiled masturbation. Admitted to Filadelfia on 25/8-1954.

Objective findings. Dysplastic with a fat, premature trunk, especially hypertrophic mammae, but slender extremities with small hands and feet. Strong spasticity in upper and lower extremities. Further details in the neurological examination could not be demonstrated on account of her dementia.



Pedigree of Cases 1 and 2.

Ophthalmoscopy showed typical retinitis pigmentosa.

Laboratory findings normal except for vacuoles in a great part of the lymphocytes.



Pedigree of Case 3.

Case No. 3.

Female born 19/6-1936. Philadelphia J. 31.510.

Only child in a healthy family. Born by delivery with forceps, one month before time. Her weight at birth was two kilogrammes, but her development was quite normal, until her sight in her seventh year began to fail. At ten years old she was blind and at the same time epileptic petit mal and grand mal started, combined with progressive dementia. Her menstruation started normally in her fourteenth year, but has been very scarce. Admitted to Philadelphia 27/2-1954.

PEDIGREE SYMBOLS

- Proband.
- Not examined.
- ▤ Vacuoles found in the lymphocytes.
- ▥ Vacuoles not found in the lymphocytes.
- ▧ Inhomogenities in the protoplasm of the lymphocytes.
- ⊠ Stillborn.
- ◻ Neurological or psychiatric disorders.
- Male.
- Female.
- Sex not known.

Now, eighteen years old, she is almost constantly bed-ridden. She plays a little with dolls, but otherwise shows no spontaneous activities. She is completely blind without light-sensation.

Objective findings: Slight dysplasia. Head and trunk normally developed, but hands and feet small and infantile. Marked spasticity in all four extremities. Tendon reflexes abolished. Further details could not be revealed, owing to her compact dementia. Spastic atactic gait and only with assistance of her nurse.

Ophthalmoscopy shows typical retinitis pigmentosa, atrophic papillae and very slender blood-vessels.

Ordinary laboratory findings displayed no abnormalities beyond vacuoles in a great part of the lymphocytes.

Case No. 4.

Male born 25/7-1936. Filadelfia J. 31. 711.

His father is excessively neurotic. Otherwise healthy ancestors; number one of two (see Case 5).

He was born one month before time, but developed normally until three to four years old he grew more and more dim-sighted and in the course of four years nearly blind.

Retinitis pigmentosa was found, and simultaneously a decrease in his psychic functions took place. During the following years he was restless, uneasy, and tiresome for his parents and nurses on account of excessive loquacity.

At thirteen years old he had periods of anxiety and hallucinations. He complained of buzzing and knocking in his head, and during some weeks his head had a compulsory inclination to the left. He gained more than normal in weight although his somatic development was retarded, and he had several epileptic convulsions returning irregularly in spite of ordinary antispasmodics. Admitted to Filadelfia on 23/4-1954.

Objective findings: obesity and left-sided cryptorchidism. Questionable left-sided facial palsy. The left plantar reflex showed extensor response. The remaining neurological examination did not show any abnormalities.

Ophthalmoscopy: Typical retinitis pigmentosa.

Electro-encephalography: General dysrhythmia of medium degree.

Encephalography: General enlargement of the ventricles, but in particular of the left.

Laboratory examinations showed vacuoles in the lymphocytes. Otherwise normal findings in the spinal fluid, blood, and urine.



Pedigree for Cases 4 and 5.

Case No. 5.

Female born 15/3-1938.

Only sister of the patient, Filadelfia J. 31.711, identical with Case 4.

She was normal at birth and during growth. At school she was the head-girl.

At nine years old her vision began to fail, and soon afterwards she was sent to an institution for the blind. At ten years old her mental health was injured. She became hot-headed, with lacking concentration, anxiety, hallucinations, excessive loquacity, and aggressiveness. First menstruation at fourteen years old. At fifteen years old her intelligence quotient was only 60 per cent, and she was admitted to Ehberødgård (hospital for feeble-minded) on 12/9-1953.

Since then a further reduction of her mental abilities has taken place. Six general epileptic convulsions have been observed.

Ophthalmoscopy: Typical retinitis pigmentosa.

Objective neurological examinations: Normal findings.

Ordinary laboratory examinations: Vacuoles in a great part of the lymphocytes. Otherwise no abnormalities could be found.



Pedigree of Case 6.

Case No. 6.

Female born 31/7-1930, Filadelfia J. 21.006.

Family history. Mother: Convulsions fourteen to fifteen years old. A maternal uncle suffered from muscular dystrophy. Otherwise healthy ancestry.

She is the third of five. Two are healthy; one was still-born and one has later got amaurotic idiocy.

Normal at birth; weight: three and a half kilogrammes.

She developed normally. No children's diseases.

At seven years old her sight began to fail.

At nine years old her mentality worsened, her intelligence diminished and epileptic convulsions occurred singly or several times a day. At twelve years old she was admitted to Nyborg Hospital for epileptic children. Here her I.Q. was found to be sixty-two per cent. *H. Ehlers, M.D.*, found a heredo-degeneratio maculae luteae; and further her vision was reduced to one eighteenth.

Menstruation normal from her fourteenth year.

At fifteen years old transferred to Filadelfia.

Neurological examination revealed a right-sided hemihypoplasia and dysplastic habitus with infantile face and extremities and a trunk with a round fat belly like a doll.

In periods choreatic movements of her head and upper extremities, and a slight ataxia of her right upper and lower extremities. Her gait marked by slight right-sided hemiplegia. Details could not be ascertained on account of her dementia.

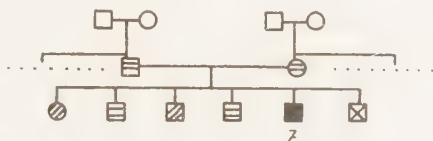
Ordinary laboratory examinations showed normal findings in the cerebrospinal fluid, blood and urine; but at that time we did not search for vacuoles in the lymphocytes.

Encephalography: Slight dilatations of both ventricles and slight atrophy of the cortex, especially in the frontal regions.

Electro-encephalography: Marked diffuse dysrhythmia and series of three c/s spikes-and-waves in all leads lasting four to nine seconds. The last two years she was often extremely anxious, screaming and hallucinated in spite of all medications.

A cardiazol-shock was tried in order to stop her anxiety and restlessness. The result was good for one day; but the next she got four strong epileptic convulsions. She was rather exhausted by these and died seven days later.

Postmortem examination of the brain by *Erna Christensen*, M.D., showed macroscopically only a slight veiling of the leptomeninges on the convexity. By microscopy were found signs of meningo-encephalitis basalis and ependymitis granularis incipiens ventriculi tertii, furthermore deposition of lipofuchsin in the ganglion cells, and especially in the great pyramid cells in the premotor cortical regions, where the nuclei are eccentrically placed.



Pedigree of Case 7.

Case No. 7.

Male born 1935, treated at Rikshospitalet, Neurol. Dep., Oslo 1951.

Family history. His father's brother died insane. Two of his mother's sisters died from tuberculosis. Youngest of six. One was still-born; the rest are healthy.

Normal at birth. At one year old he was treated for a haemangioma on the trunk. At two years old morbilli m.g. with febrile confusions for one day and night.

At four years old a questionable cerebral concussion without demonstrable sequelae.

At five years old he grew dim-sighted. After three years he was almost completely blind.

At seven years of age his speech was more and more unintelligible and simultaneously epileptic fits started.

He tried in vain to follow ordinary school and later education in an institution for blind children.

From his fifteenth year his dementia has steadily increased so that at nineteen years old he only has the intelligence of a two years' child.

At the Rikshospital in 1951 was found:

Typical degeneratio pigmentosa retinae. Only bilateral light-sense is preserved.

His speech is undistinct and stammering. His posture is slack with a slight thoracic kyphosis.

Encephalography: normal.

EEG: Generally wide-spread 3 c/s spikes-and-waves although in several ways different from the cryptogenetic classic petit mal curves. In the left occipital region isolated spike-and-wave complexes perhaps indicate epileptigenous focus.

Ordinary laboratory findings were all normal.

Blood examination 1954 with the assistance of Dr. Krohn, Oslo, and Dr. Palmer, Drammen, showed vacuoles in the lymphocytes as well as in the blood from 4 of 6 relatives examined.

Case No. 8.

Female born 1/2-1906, died 14/7-1941. Filadelfia J. 8545.

Family history: Father had cramps and his brother alcoholic psychosis. (Her

sister cf. Case 9). Number one of four. Number two the said sister; number three and four are healthy.

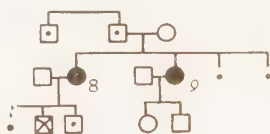
Normal at birth and during growth. During her first pregnancy she got epileptic convulsions, which were repeated with increasing frequency. Her delivery was normal and the child, now twenty-eight years old is healthy. Her next pregnancy two years later was terminated with a still-born monster. During this pregnancy her epilepsy advanced. Two years later again, during her third pregnancy, she had still more fits and her sight was impaired. The birth was normal, but the child died six weeks old in cramps.

After the last delivery she grew mentally defect, hard-bitten, querulous, and gradually demented. Admitted to Filadelfia 27/2-1934 for treatment of her epilepsy. After four months she was discharged. Normal neurological findings, but ophthalmoscopy showed moderate retinal degeneration, and her vision was correspondingly impaired. A year later she returned to the hospital and died here seven years later in cachexia, thirty-five years old.

During the last year she had groups of excessive general convulsions. Her sight was reduced to slight light-vision and ophthalmoscopy now presented typical retinitis pigmentosa with slender blood-vessels, turbid chorioidea and excessive atrophiea nervi optici.

Ordinary laboratory findings were all normal. Unfortunately blood-examinations were performed without any special regard to the lymphocytes.

Postmortem examination revealed a tuberculous affection of the right lung, and a slight dilatation of the brain-ventricles. By mistake no histological examination of the brain was done.



Pedigree of Cases 8 and 9.

Case No. 9.

Female born 7/12-1911, died 7/7 1954. Filadelfia J. 27.402.

Family history as Case 8. Number two of four, cf. Case 8.

She was quite normal and healthy until her first pregnancy twenty three years old. During the pregnancy she complained of headache, impaired vision, and several epileptic fits. The daughter now 15 years old quite normal.

The following year her vision failed further, and her mind altered. Her faculties were reduced, she was irritable, morose, and scolding. On account of this and atrophiea nervi optici a cerebral tumour was suspected. But an explorative craniotomy revealed no abnormalities.

At twenty-six years old, during her second pregnancy and after a normal birth, her epilepsy was intensified, so that she had fits almost every day; and after an accumulation of fits, she was almost comatose for eight days, was admitted to Middelfart Mental Hospital, and transferred to Filadelfia for treatment of her epilepsy in 1948. The son, now 12 years old, is quite normal.

No neurological abnormalities were found.

Encephalography showed normal findings.

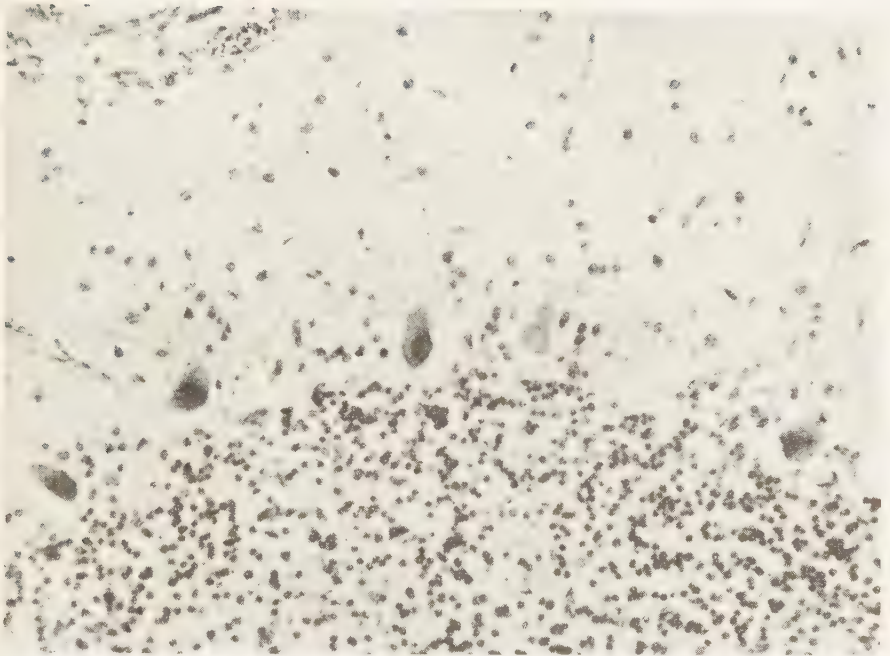


Fig. 3 a.
Cerebellum.

Degeneration and lipoidosis of the Purkinje cells (and one ghost-cell). Pronounced failing of cells in the stratum of Purkinje and moderate failing in the stratum granulosum.

(Staining with galloeyanin. K. A. Lorentzen, M.D.).

EEG displayed strong diffuse dysrhythmia.

At ordinary laboratory examinations the only pathological findings were vacuoles in a great number of the lymphocytes.

In the hospital her epileptic fits returned irregularly with typical general convulsions. She went more and more demented, blind, atactic, and spastic, and died, 43 years old, after three excessive fits within three hours.

Postmortem examination of the brain by K. A. Lorentzen, M.D., showed considerable deposition of lipoids in the Purkinje cells of the cerebellum and hippocampus combined with an apparent degeneration of the nerve-cells (Fig. 3). Lipoid deposition to a very slight degree was found almost everywhere in the brain. The glia was moderately changed, but no fibrillary gliosis was observed.

The lipoids in the cerebellum and hippocampus stained deeply red with Fettrot and they must therefore partly consist of neutral triglycerides. In other slices the dyeing is red-yellow or golden, perhaps indicating the presence of cholesterines.

Neither degeneration of the myelin-sheaths nor inflammatory or vascular disturbances could be demonstrated anywhere in the brain.

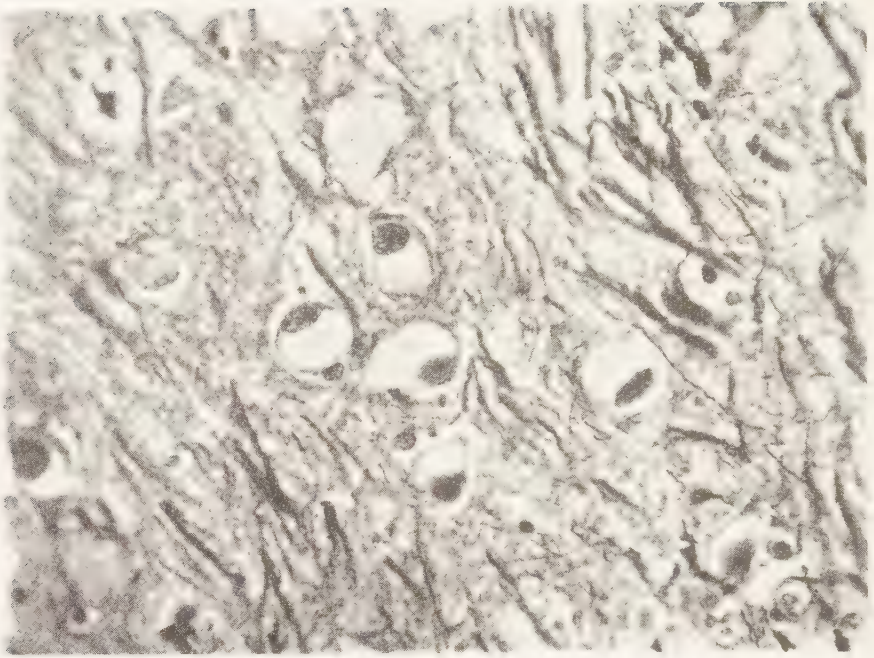
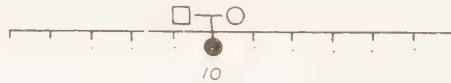


Fig. 3 b.

Hippocampus.

Strongly puffed nerve cells with hyperchromatic and eccentric nuclei. Neurofibrils have nearly completely disappeared.

(K. A. Lorentzen, M.D.).



Pedigree of Case 10.

Case No. 10.

Female born 5/1-98. Philadelphia J. 10.224.

Family history. Number six of eleven. Number nine is night-blind. All the rest are healthy, as well as her parents and their ten brothers and sisters.

Normal at birth, but her development was retarded both mentally and bodily. She walked late and never managed to talk plainly.

Her first menstruation appeared at twelve years of age. Simultaneously epileptic convulsions started and her temper changed. She became irritable and aggressive.

The following years her hearing and sight were impaired and her dementia increased.

At thirty-eight years old retinitis pigmentosa was found and the following year she got a transitory left-sided hemiplegia. At forty-three years old she suffered from acute pellagra without influence on her earlier symptoms.

Her epilepsy continued with petit mal and grand mal some few times a year.

Neurological examination now shows a dysplastic habitus, general slight spasticity, dysarthric dysphasia, amaurosis, and hypacusis of the internal otitis type. Her mentality is impressed by her dementia and long-lasting hospitalisation.

Ordinary laboratory examinations showed vacuoles in a great number of the lymphocytes, but otherwise normal findings.

Case No. 11.

Female born 27/2-1936. Filadelfia J. 27.649.

Family history. Her grandfather died from cerebrospinal lucs. Otherwise healthy family. Only child, born in due time. Weight only two kilogrammes.

She remained slender and slack, developed slowly, and at six months old got eczema, which persisted for six years.

At two years old a slight hemiplegia and retarded development of the right side of her body were observed.

No children's diseases, but mentally she was retarded and could not follow ordinary teaching.

At eleven years old general epileptic fits started. At thirteen years old she had an accident with concussion and fractura basis cranii, but without demonstrable consequences.



Pedigree of Case 11.

At fourteen years old at the Children's Dep. of Rigshospitalet encephalography showed normal findings. EEG showed dysrhythmia of medium degree, but no focal signs. Her intelligence-quotient was sixty-four per cent.

At fifteen years old she was admitted to Filadelfia (30/4 1951) for treatment of her epilepsy.

Her first menstruation appeared at fifteen years old and has since then been normal. Examinations have not shown any new symptoms except in her EEG, where the dysrhythmia is more pronounced and series of 3 c/s spikes-and-waves lasting for 1-3 sec. are seen in all leads. Her appearance is like a doll or Alice from Wonderland with immature traits especially of her face, hands, and feet, which are very small and slender.

Ophthalmoscopy and test of her vision showed normal findings. (*Steen-Hanum*, M.D.).

Her mentality is childish as that of a four-year old child.

Ordinary laboratory findings are all normal except in the blood, where vacuoles are found in 7 per cent. of the lymphocytes. In all lymphocytes without vacuoles the protoplasm was quite inhomogeneous.

COMMENT

Eleven cases of so-called lipoidoses are reported. Of these the first seven cases precisely correspond to the classical description of mb. *Spielmeyer-Vogt*.

Cases 8 and 9, starting in the second decade of life, agree with *Kufs'* disease; but they differ from this by the fact that they got their first symptoms during their first pregnancy. Furthermore, severe deterioration during the following pregnancies was observed.

Case 10 is atypical, starting in early childhood, but progressing so slowly that the patient is still alive fifty-six years old; although her state, bodily as well as mentally, is strongly reduced.

In Case 11 the patient has hitherto had no complaints from her eyes, though her dystrophies in other organs have been manifest for at least sixteen years.

All the eleven patients have had epileptic paroxysms, grand mal or petit mal, which do not in any way disagree with fits seen in cases of cryptogenic epilepsy.

All were obviously mentally reduced; in most cases evidently increasingly demented.

All had diffuse neurological symptoms as well of a pyramidal as of an extrapyramidal character.

Six of the patients had transient psychotic symptoms, with hallucinations, anxiety, aggressiveness, or the like.

The most marked symptom in all eleven patients is somatic dysplasia and dystrophy, probably owing either to a primary deficient development or to a progressing destruction of the structure and function of the cells in the reticulo-endothelial and the central-nervous system.

The fact that our material consists of nine female and only two male patients must be accidental. The literature comprising several hundreds of cases has no difference between the sexes.

Our eleven patients are too few for a statistical evaluation of hereditary factors, but that heredity is of evident importance appears even from our cases where three pairs are brothers and sisters and two more have sisters suffering from juvenile amaurotic idiocy.

The most interesting hereditary factor, however, is the abnormal vacuoles in the lymphocytes found not only in nine cases of j.a.i., but even in the blood from several of their normal relatives.

We hope that it will be possible to make a thorough exploration in institutions and homes for blind, feeble-minded, and epileptic patients. Most certainly a considerable number of patients will be found there.

suffering from one or other of the forms of lipoidoses. With a sufficient large material of patients where the clinical diagnosis is ascertained, it must be possible in cooperation with the Institute for Hereditary Biology of the University of Copenhagen to collect pedigrees, as *Sjögren* has made it in Sweden, sufficiently comprehensive for hereditary examinations in Denmark as well.

In this way we hope to find out if the hereditary factor for vacuoles in the lymphocytes also depends upon a monohybrid recessive factor as *Sjögren* claims it for juvenile amaurotic idiocy.

At ordinary examinations of smears from the patients, the vacuoles in the lymphocytes were easily found. Some cytochemical investigations of the lymphocytes were carried out, and we have found some abnormal variations in their content of neutral fat, ribonucleinic acid and alkalic phosphatase.

The cytochemical studies are in progress and further details will be published.

We intend to extend our investigations to as many as possible of the relatives of the patient, or in any case a sufficient number to ascertain the hereditary traits of this blood anomaly.

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A PROBLEM OF SIMULATION IN MODERN LEGAL PSYCHIATRY

By

GEORG K. STÜRUP

Some 20 years ago, Krabbe registered surprise when a young neurological colleague wanted to specialize in psychiatry. Even at that time the task of the psychiatrist in the mental hospital might—from the neurologist's standpoint—be regarded as that of the turnkey: he made certain that the patient remained in the hospital and was taken care of.

Since then, psychiatry has taken up the struggle for an equal position among the other branches of medicine. Clinically and therapeutically orientated legal psychiatry has been successfully established within prison work.

Whereas the essential object of classic legal psychiatry is to determine whether or not an accused may be unsuited to be subjected to one or another form of repression laid down by law—and to examine how the defendant's psychic state fits in with the more or less clearly defined criteria established by law or by common usage—the therapeutically working legal psychiatry is fully and exclusively based on classic medicine.

For this new branch it is first and foremost necessary to concentrate on the general features: The patient's personality and his attitude towards himself and towards society is the central field of action. By all accessible means and possibilities it is necessary to make him realize his position and circumstances in such a manner that he does not lapse into the pessimistic feeling of inferiority which has made him a constant danger to law and order.

Treatment of possible brain diseases or medical complaints is equally as important as treatment against alcoholism, re-training for work, educational and cultural influence, and direct psychiatric psychotherapy.

But at the same time one must cooperate with the law-enforcing authorities in maintaining society's justified demand for protection

against the inconveniences and dangers which established convicts at large would represent.

The problem of simulation—important also to neurology—is, however, one of the constantly recurring main problems of legal psychiatry, coloured as it is by the special atmosphere in which the symptoms develop: simulation may even dominate the whole picture, thereby completely obscuring and upsetting the therapeutic programme.

From a dynamic-psychiatric point of view it is natural to suppose that particularly heavy psychic loads will result in particular manifestations, frequently with at the same time simulatory and hysterical traits. It is therefore not surprising that the Danish quislings with death sentences could present a number of mental states more or less unknown to our legal psychiatry and calling for considerable diagnostic skill.

Capital punishment had for a number of years (since 1930) been abolished in Danish Penal Law. The last execution had been carried out in 1892. The special enactments concerning quisling activities during the German occupation reintroduced capital punishment in respect to the most severe of these crimes. It was unanimously agreed that these new cases of death sentences were legally prepared and investigated as thoroughly as humanly possible. They were all referred to the Supreme Court and, finally, the problem of possible mercy was thoroughly investigated by the Ministry of Justice.

This long proces, requiring much time, may in each department of authority dealing with the cases have eased the feeling of personal responsibility for this ultimate measure. But it also involved a deplorable further mental stress on the prisoners in question. Those with the most serious and comprehensive list of crimes were not finally sentenced until after several years' imprisonment.

Thus these persons had been exposed to an extremely severe psychic stress. When first arrested, they had to expect a possible death sentence. Moreover, in one court after another, they now had to follow the trials and experience the excitements before sentences were passed. After the Supreme Court sentence, the prisoner had to continue to wait in an increasingly desperate position. Up to the last moment the majority hoped to be one of the not very few sentenced prisoners who were reprieved and sent to gaol. Despite this situation there were only few who did not withstand this stress. Such cases are of especial psychiatric interest.

"A" had voluntarily joined up as a soldier, urged by a certain amount of juvenile idealism and desire to make an effort. During his period at the front, he exhibited a certain egocentricity and vanity.

His personal relation to and the respect of his fellow-soldiers meant much to him. In addition, there is no doubt that he had been disappointed in his idealism. He had had occasion to observe Nazism in practice (a blow to his expectations), and, moreover, he was disappointed in the manner in which he had participated in its work and in being able himself to commit the acts he actually did after having returned from the front.

He passed through the Low and High Court proceedings. The psychiatric report (by the full-time psychiatrist appointed by the Ministry of Justice for the investigation of criminal cases), issued after prolonged observation prior to the trial in the Low Court, describes him as a psychopath of the weak-willed, emotionally unstable and somewhat nervous type. It is further emphasized that after being arrested he had developed a nervous state of depression which, with regard to the circumstances, could hardly be supposed to go beyond the limits of a normal reaction to his situation. He was therefore deemed to be "a person likely to benefit from punishment". Prior to the High Court proceedings the psychiatrist upheld this evaluation, and hospitalization was not considered necessary.

After this second sentence he was very self-reproachful. He talked of the vanity which had carried him into actions which had resulted in severe criminality. He was unhappy about the misery he had caused others, and he took every opportunity to assert that he had never been a coward.

During the following period he developed the idea that his wife, who visited him regularly every week, was pursued by the prison staff. When sternly talked to he might abandon these ideas, although they gradually took the form of voices, and thereafter he turned humble and miserable, seeking comfort and help.

While his case was before the Supreme Court he started to question his identity. He was not "A". At times he appeared self-secure and confident, and at other times insecure and cowed dependant upon the manner in which he was addressed at the moment. The Defence maintained that he had become insane, and a week after the Supreme Court sentence had been passed, the psychiatrist who had previously examined him, after another interview in the prison (on a Sunday), stated that the prisoner suffered from prison psychosis, i.e. a state of hysteric insanity (Ganser's syndrome). To the brief statement was added: "There is in my opinion no simulation, but the prisoner is insane".

Against this was the certificate by the prison medical officer who was not a psychiatrist but who had had the opportunity of watching

the prisoner's state from day to day. He stated "that the acts on the part of the prisoner have always appeared construed and during the last months have been a willed effort to avoid execution".

The medico-legal problem was now whether he suffered from insanity to a degree that warranted postponement of the sentence's being carried out.

For a few days he was admitted to an ordinary psychiatric hospital ward. Here it was very difficult to establish contact with him. One of these days he was completely dumb. It was supposed to be a hysterically simulated muteness. Now and then he would speak, apparently only with the motive of being helpful to the guards.

On admission to the psychiatric observation ward of the prison system he was passive and reluctant, with a tense, quivering expression; he answered with either the English "Oh, yes", or the Swedish "Det vet jag inte" (I don't know). By a strongly suggestive conversation it was, however, possible to make him answer in plain Danish. He absolutely denied being afraid, but was hesitant in his "no" to the question of whether he might be afraid without realizing it.

Although he did not expressly admit it, he gave the impression of full orientation. He displays a pronounced requirement for contact and a fairly evident suggestibility. On this background it was fairly easy to make him adequately relaxed during a conversation, and in a quiet manner he realized that he must write his wife and thereby finish in a proper manner. Several times he said that he realized that "he must shoot himself", but when pinned down to this statement he was well aware that others were going to shoot him. He constantly used terms as "it shall be brought to an end", or that he would "do the right thing, it is difficult".

He dictated a letter to his mother, dead long ago, ending up with a statement that he had considered the matter carefully and continued "I would prefer to be discharged from the hospital, home to you. You can help me to find the right way"; later in that same day he maintained that he was not identical with the man whose name he bore—"I cannot possibly be, he is gone".

Later he delivered a long speech in defence of the person he was no longer. The urge to abandon his personality he also demonstrated by brusquely demanding his own clothes whereupon he began taking off his suit. When firmly told to keep his clothes on he willingly abandoned this idea and was easy to engage in conversation.

On the following day he attempted to identify himself completely with the physician—to the point of wanting to borrow his glasses and watch.

During induced relaxation he passed into a light hypnotic state and then willingly agreed to speak naturally; with tears in his eyes he later maintains that he well realized his situation.

During the evening he was repeatedly whimpering and unhappy. A visit by his wife was without incident, although naturally marked by the extremely severe stress on both.

There is hardly any doubt that a number of the described manifestations were on the conscious level, i.e. the use of English and Swedish, avoiding German, and the periods of muteness, while other reactions were equally certainly automatic, without his willed intention. Applying the criterion of consciousness on this distinction we are dealing with simulatory as well as hysteric reactions proper.

Members of the Medico-legal Council, after they had had the opportunity of observing him in the one as well as in the other phase, fast changing from the one to the other depending on whether he was interviewed or left alone, agreed to the conclusion arrived at during the observation. It was stated that "after conviction he has been in a mixed state of conscious (simulatory) and unconscious (hysteric) reactions. This state, however, is not stationary but is dependant upon external influences. It can no longer be regarded as a psychosis . . ."

It was not possible to arrive at a conclusion like this regarding the case in question without complicated theoretic considerations. An attempt had to be made to draw a fairly definite line between psychotic and neurotic reactions.

As differentiating features it has been stressed (Malamud) that neuroses must not be accompanied by demonstrable organic pathology relevant to the etiology of the symptoms, there should be no primary disturbances of the mood and no persistent distortion of external reality.

Medico-legal work in such instances must necessarily build on well-defined definitions, although, from a medical point of view, there will be even transitions from one state to the other and they must be viewed as degrees of reaction.

The problem was now: to what extent must the deviation be consistent and lasting in order to justify the designation psychotic of such hysterically conditioned states? It was deemed reasonable that the state here under consideration could not be called psychotic in respect to social and legal consequences: it was possible without the use of any trick to make the patient realize and adequately assess his position - although when left to himself he relapsed into the pathologic state. He could be kept fully conscious during long interviews with the psychiatrists. By such a special form of contact which may be called

a "suitable" psychic influence he could easily be made to realize his desperate situation and react in a fairly normal emotional manner. Left to himself the personality promptly dissolved as described.

The important medico-legal line between a psychotic and a neurotic reaction has then to be: when a person subject to suitable psychic influence—as "A"—could realize reality the state should not be called a mental disease in a sense that would formally exclude the carrying out of a sentence of the one sort or another. On the basis of these considerations it was considerably easier to arrive at uniform decisions in these difficult cases.

Another case, "B", definitely a leader type, presented somewhat different problems, since the prisoner quite obviously tried to make a miserable appearance right from the moment of his arrest. He appeared for questioning with dark shadows under his eyes, made from burnt matches and cigarette ashes. From the beginning his attitude as expressed to the fellow-prisoners was: one must manage as best one can. He refused to recognize witnesses, denied all acts of torture, but according to available information he was able to remember certain points, and his memory covered varying phases. The psychiatrist dealing with him before the sentence reports how the prisoner might consider his reply and sometimes lie outright. Gradually it could not be completely disregarded that he might suffer from a hysterically conditioned loss of memory. It was clear that he well knew how to render prosecution difficult. Not only had he had the benefit of prewar personal experiences as a criminal in court, but he had also been in charge of investigations for a German-Danish group during the war.

A couple of months after he received a capital sentence in the Low Court he had been silent, withdrawn and had been removed to the prison sick ward. After this period of silence he declared that having consulted his defending counsel he had decided to stop acting and was ready to face the consequences of his deeds. It was "not the sentence but other causes" which had made him act as he had done.

Some time later he had for a period a unilateral paresis and aphonia, but the symptoms disappeared after a few days. During a third hospital admission he was restless and noisy, presenting quite a typical case of Ganser's syndrome. This state, accentuated by the confirmation of his capital sentence in the High Court, was treated by pentazole shock, with passing improvement; it was then possible to discuss the case and the severe sentence with him. During these interviews his articulation was almost normal.

Whereas on the first admission to the prison hospital he presented a picture of pure simulation, there was now a state of mixed symptoms:

pathologic elements were found together with a simulatory component. In the following period his mental state deteriorated to an even higher degree, and he was transferred to the psychiatric observation ward.

His appearance was euphoric; he gave all staff members a nickname which he used consistently. His movements and facial expression were like those of a clown. He insisted that his mother died many years ago; she was very little at the time, and he dug a small hole and put her into it. There was incontinence of feces and urine on the floor, but never in bed. In between he was affected by the reactions of the prison staff or his fellow-prisoners. During a period he yelled very loudly. Attempts were made to obtain better contact with him through narco-analysis. He then admitted to suffer "there is so much". He reproached the physician indicating that he definitely did not like him: it is obvious that he was aware that he was talking to the superintendent. His language is that of an infant, but in single instances, especially when awakening after injections of amytal he used generalisations. In a single instance he threatened the staff with complaining to what he called the "death doctor", i.e. the superintendent, because he has had to read the High Court sentence to him. Thereafter he has repeatedly stated that "the death doctor wants me to die when I get well".

Thus, the clinical picture in many ways may resemble that of the first-mentioned case. At times there was a certain element of Ganser-symptoms, whereas during other periods there was a clear element of simulation which was maintained during several years—an unusually long period—and unusually consistently.

None of these features was surprising in view of the personality strength he had displayed during his criminal period. In spite of the clownish consistency which he could not be made to abandon, it was the common opinion that he was certainly in a predominantly simulating state, opposed to attempts at treatment of a medical nature. His behavior on the day before execution when he took leave of his relatives in a rather natural way, confirmed that his was a case of simulation.

Although medical opinion in this case has been unanimous in the correctness of the diagnosis, it should not be forgotten that the psychiatric diagnosing in such cases moves in a field that calls for the utmost vigilance. Not until it is too late does it become known whether or not a decisive error has been made.

Now capital punishment is once more unknown in Denmark. The psychiatric experiences during the few years when it was in force—in respect to the severest torturers and traitors, a very limited group of criminal offenders—were of such a nature that the psychiatrist

must feel relief at the prospect not having to decide such diagnostic problems in the future.

The period under consideration revealed that all parties concerned were subject to unusual emotional influence. In addition, even the psychiatrist found it exceedingly difficult, not to say impossible, to retain his professional objectivity and to refrain from yielding to the emotional stress resulting from his knowledge of the outcome of his diagnosis of the case.

Should the future involve risks of being faced with similar medico-legal questions which are in direct conflict with the codes of treatment—which can and should be the central point also of psychiatrists working in penal institutions—the author would simply prefer to leave this field of work and dissuade others from exposing themselves to the personal stress involved in these activities.

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DYSPLASIA FIBROSA OSSIIUM

*With Special Reference to Lesions of the Skull and
the Vertebral Column*

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INTRODUCTION

Dysplasia fibrosa ossium is probably one of the commonest congenital anomalies of the development of bone. It is, however, a rare disease. It seems to be the result of a perverted activity of the specific bone-forming mesenchyme, involving one or many bones, and accordingly it is classified as monostotic or polystotic fibrous dysplasia of bone.

It sometimes coincides with other anomalies and dysfunctions, the main ones being the following:

- Abnormal pigmentation of the skin.
- Premature sexual development in females.
- Hyperthyreoidism.
- Coarctation of the aorta.
- A rudimentary kidney.
- Multiple arterio-venous aneurysms in the extremities.

These extraskeletal abnormalities seem to be found almost exclusively in connection with the severe forms of the disease, suggesting a more far-reaching developmental anomaly.

The central feature of the disease, however, is the changes or lesions of bone, which are present in every case. The normal tendency of the mesenchyme towards ossification seems to be interfered with by some local disturbance, but the etiology is obscure.

Dysplasia fibrosa ossium is a clinical entity, which during recent years has been separated from the pathological conditions formerly classified as osteitis fibrosa cystica generalisata or von Recklinghausen's disease of bone, but it has also been confounded with other diseases affecting the skeletal system.

Jaffe has pointed out that many terms have been used in the

literature to describe dysplasia fibrosa ossium, such as "osteodystrophia fibrosa unilateralis, unilateral polyostotic osteitis fibrosa, unilateral Recklinghausen's disease, osteodystrophia fibrosa cystica generalisata limited to one side of the body, focal osteitis fibrosa, osteitis fibrosa in multiple foci, osteitis fibrosa with formation of hyaline cartilage and osteitis fibrosa disseminata."

Lichtenstein and *Jaffe* were able to find thirty-three titles under which this disease has been described, but they were mainly variations on the theme of "osteitis fibrosa" or "osteodystrophia fibrosa."

In 1937 *Albright* and his co-workers described a "syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females." Dysplasia fibrosa ossium is often described, even in textbooks of diseases of bone, under the name of *Albright's disease*. This name, I feel, should be reserved for such cases, only, in which all the signs and symptoms, constituting the syndrome described by *Albright*, are found. In addition it should be pointed out that in 1922 *Weil* had described the coincidence of disturbed bone growth with abnormal fragility of bone and *pubertas praecox*.

In 1934 *Borak* and *Doll* described a similar case, and in the same year *Goldhamer* reported a case with osteodystrophia unilateralis, *pubertas praecox*, and hyperpigmentation of the skin.

In 1942 *Lichtenstein* and *Jaffe* made an excellent review of this disease, based on the findings in 90 cases, 23 of which were cases in which a microscopic examination of tissue from bone lesions had been made by the authors, and, furthermore, they had at their disposal the history, the clinical findings, and the roentgenograms in each case.

In 87 of the cases reviewed by *Lichtenstein* and *Jaffe* the extent and localisation of the bone lesions was clearly known. In 15 cases the disease was monostotic, i.e. affecting only one bone. In the remaining cases it was polyostotic, affecting several or many bones, as a rule predominantly onesided in distribution. In 6 out of the 23 cases that *Lichtenstein* and *Jaffe* had examined personally, the skull was affected. They point out that in the calvarium a focus of dysplasia fibrosa may cause a localized, sometimes quite prominent, expansion of the outer table, and a striking thickening and opacity of the base of the skull, especially around the pituitary fossa, are often found. This is in good agreement with the findings of *Albright* and associates, *McCune* and *Bruch*, and several other authors.

The facial bones are often strikingly deformed, and affection of the vertebral column is by no means uncommon, causing compression of one or more vertebrae in some of the cases.

Schlumberger made an extensive study of the monostotic cases at the Army Institute of Pathology, and reported on 67 cases of dysplasia fibrosa involving a single bone.

The regional distribution of the lesions was as follows: costa 29, femur 9, tibia 8, maxilla 7, calvarium 5, mandibula 2, humerus 2, ulna 2, vertebra 1, pelvis 1, fibula 1.

Schlumberger was able to find only two cases in which the disease affected more than one bone, and his series shows beyond any doubt how frequently the calvarium and the facial bones are involved, even in monostotic cases.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The disease manifests itself in childhood or adolescence in the more severe cases, but where the involvement is very localized it may run a quiet course until adult life. It is more frequent in women than in men, the ratio being about 3 to 1.

The common *clinical signs and symptoms* which cause the patients to seek treatment, are pathological fractures, limp, pain, soreness, or stiffness, shortening of a lower extremity and deformity of the affected area or areas.

The symptoms are often of long duration, a fact suggesting the chronicity and the slow progression of the disease.

In severe cases the skeletal lesions may be accompanied by sexual and somatic precocity in females, areas of cutaneous pigmentation in both sexes and hyperthyreoidism. Even other abnormalities have been reported in single cases, as mentioned above.

The roentgenographic findings have been summarized by *Lichtenstein* as follows: "(1) broadening or expansion of the bone; (2) thinning of the cortex; (3) characteristic rarefied and apparently trabeculated appearance, usually erroneously interpreted as indicating "cystic disease", and (4) secondary deformities of affected bones."

The histological picture has been described by *Lichtenstein* and by *Lichtenstein* and *Jaffe*. Again I quote *Lichtenstein*:

"Thinning of the cortical bone, which may eventually be reduced to a thin expanded shell, is due in part to resorption but largely also to erosion of the endosteal surface by the proliferating fibrous tissue. There is, however, no gross or microscopic evidence of periosteal deposition of new bone, except in connection with callus at the site of spontaneous infractions of the cortex. The substantia spongiosa and also the marrow of affected bones are replaced by fibrous tissue. The latter is composed of spindle cells with oval, pale-staining nuclei and indistinct cytoplasmic outline. The basic connective tissue may in some areas be fairly cellular, while in other areas, on the contrary, there may be a fibroblastic dif-

ferentiation with a formation of bundles of mature connective tissue, rich in collagen. Special stains for detecting lipid gave negative results. The stroma may be infiltrated by a few small lymphocytes and mononuclear cells.

Dispersed within the fibrous tissue without following any definite pattern, there are small trabeculae of primitive, poorly calcified new bone of variable size and contour. They are apparently developed by osseous metaplasia, without the mediacy of osteoblasts. In the relatively avascular fibrous areas the trabeculae tend to be sparse in distribution; in the more vascular areas there is usually more extensive deposition of osteoid material and fiber bone. Some of the trabeculae show Howship's lacunas lodging osteoclasts, but on the whole there is comparatively little evidence of osteoclastic resorption. Deposition of calcium within the primitive new bone is variable in extent and distribution. Generally speaking, the bone is calcified poorly and in an imperfect spotty fashion.

The basic fibrous tissue, on the whole, is relatively avascular, showing only occasional thin-walled vascular spaces. In some areas, however, it may be permeated by a moderate number of capillaries and even occasional small arterioles. Many of the blood vessels are in close proximity to the trabeculae of the bone. The latter are frequently surrounded by slender spaces which because of their endothelium-like lining suggest vascular spaces. Some capillaries appear empty, while others are congested and show small perivascular extravasations of blood. The presence of granules of hemosiderin within phagocytes indicates previous capillary hemorrhages which have been resorbed. In their vicinity one may also encounter small nests of giant cells, resembling osteoclasts.—Sporadic islands of hyaline cartilage may also occur within the fibrous tissue, although this is not constantly observed. The cartilage tends to become calcified, especially at its periphery."

For further details of the macroscopic and microscopic appearance of the lesions the original papers by *Lichtenstein* and by *Lichtenstein* and *Jaffe* should be consulted.

The chemistry of the blood has shown some increase in alkaline phosphatase activity in a number of cases, the highest values being found where the tendency to formation of new bone within the fibrous tissue was most pronounced. The calcium content of the blood serum has been found to be essentially normal, with the exception of a few cases in which it was perhaps slightly elevated. Estimations of inorganic serum phosphorus have shown normal values.

It should be pointed out that malignant transformation of the lesions has been reported in four cases according to *Coley*. The disease is neither hereditary nor familial.

DIFFERENTIAL DIAGNOSIS

A great number of diseases may come into consideration before the final diagnosis of dysplasia fibrosa ossium has been made, depending for instance on the age of the patient and the localisation of the lesion or lesions. If, on the other hand, one is familiar with the

roentgenological and, above all, with the histological picture and secures a biopsy specimen, a correct diagnosis should be arrived at.

The common pitfalls shall now be mentioned briefly.

1. *Hyperparathyreoidism* (*Osteitis fibrosa cystica generalisata*).

In the past dysplasia fibrosa ossium has repeatedly been diagnosed as hyperparathyreoidism. The roentgenographic picture of the lesions may be similar, but it should be kept in mind, that *in dysplasia fibrosa ossium the unaffected bones are normal in appearance*. They do not show any osteoporosis, and the disease is predominantly unilateral. There are no signs of renal involvement or calcinosis elsewhere, the blood calcium is normal in most cases and only slightly elevated in others, blood phosphorus is normal, and the output of calcium in the urine is not increased. Alkaline phosphatase, however, may be somewhat increased in some cases. Careful study of the blood chemistry and microscopic study of material from a bone lesion should secure a correct diagnosis.

2. *Hand-Schüller-Christian's* disease, is another possibility, especially in children with severe involvement of the skull. It should be pointed out that exophthalmus may occur in cases of dysplasia fibrosa, but diabetes insipidus has not been reported so far. If Hand-Schüller-Christian's disease cannot be ruled out on clinical grounds, biopsy will give the correct answer.

3. *Dyschondroplasia* or *Ollier's* disease may be considered in certain cases as the osseous involvement may be predominantly unilateral. In doubtful cases biopsy will establish the diagnosis.

Other pathological conditions which should be kept in mind include: Sarcoma, osteoid osteoma, benign giant cell tumor, non-osteogenic fibroma, bone cysts, eosinophilic granuloma, Paget's disease, multiple myeloma, and leontiasis ossea, which is, however, only an old descriptive name and not a clinical entity. All these conditions can be ruled out by careful clinical, roentgenographic and microscopic study.

REPORT OF A CASE

In March 1954 I had an opportunity to study a case of dysplasia fibrosa ossium in the Medical Department of the Landspítali Islands (Icelandic State Hospital), Reykjavík.

The patient was a female, A. S., born 15th April 1922. In the beginning of the year 1934, then about 12 years old, she noted protrusion of the left eye, asymmetry of the face, complained of moderate headache and got abnormally tired when reading. The patient was treated at the Finsen Institute, Copenhagen, from August 28th to September 29th, 1934.

Examination there showed exophthalmus on the left side, edema of the left papilla with prominence of 2 dioptries, the left bulbus oculi protruded outwards and downwards. There was no diplopia and vision was normal. Right eye: normal findings, and there were no signs of atrophy of the left optic nerve.

Roentgenographic examination of the left orbital region showed a very pronounced thickening of the orbital ceiling from the arcus superciliaris backwards to the fissura orbitalis superior. The medial wall of the orbita measured $2\frac{1}{2}$ cm. in thickness, protruding into the cavum nasi and dislocating the vomer and the septum over to the right side. The lateral wall was very thick also, but the floor of the orbita seemed normal. Backwards the bone changes could be followed as far back as the sella turcica, inbedding the proc. clinoides ant. and filling the sinus sphenoidalis. The structure of these bone masses was very poor. There were no signs of a destructive growth. Bioptic material was obtained from the cellulæ ethmoidales dx, which showed a somewhat fibromatous periosteal (?) tissue, and some spiculae of bone, with a somewhat loose connective tissue in between.

The pathological findings were interpreted as a tumour of the orbita, probably sarcoma, and roentgen irradiation was applied in moderate dosage.

The exophthalmus remained practically unchanged and the sight of the left eye deteriorated little by little. Some years later the patient noted a slowly increasing prominence in the left frontal and left temporal region. At the same time increasing exophthalmus sin.

In 1941 roentgenographic examination of the skull was carried out in Reykjavík, and in 1946 at the Serafimer Lasarettet in Stockholm, where the patient was admitted for examination. The roentgenographic features were very much the same on both occasions: expansion of bone in the left fronto-temporal region, and a homogenous, sclerotic bone growth, about the size of a walnut, in the planum sphenoidale and os ethmoidale on the left side, with narrowing of the left fissura orbitalis and foramen opticum and dislocation of the septum nasi over to the right side.

In addition examination at the Serafimer Lasarettet showed: Anosmia dx, hyposmia sin. Herthel: 14-15 mm dx, 23 mm sin. Visus oc. dx = 1.0, oc. sin. = 0.3. Scotoma centrale oc. sin. Fundi oculor.: edema of the papilla on the right side with 2 dioptr. protrusion; on the left side a pale, atrophic papilla was found with 3 dioptr. protrusion. The bone changes were essentially thought to suggest the diagnosis of leontiasis ossea.

The patient was readmitted to the Serafimer Lasarettet in 1947, this time for operation, which was performed by Professor Olivecrona. The inner table of the left frontal bone was resected and the ceiling of the left orbita as well. Post-operatively there was a very pronounced protrusion of the bulbus oc. sin. with lagophthalmus and keratitis, for which the patient was treated at the Karolinska Sjukhuset's Department for Eye-Diseases.

In 1951 the patient consulted Sir S. Duke-Elder of London, who thought the bone changes in the skull might be suggestive of a dysplasia fibrosa. In 1953 the left eye was removed by operation, and since then there has been no pain in the region. In the same year the patient gave birth to a healthy baby. Late in gravidity

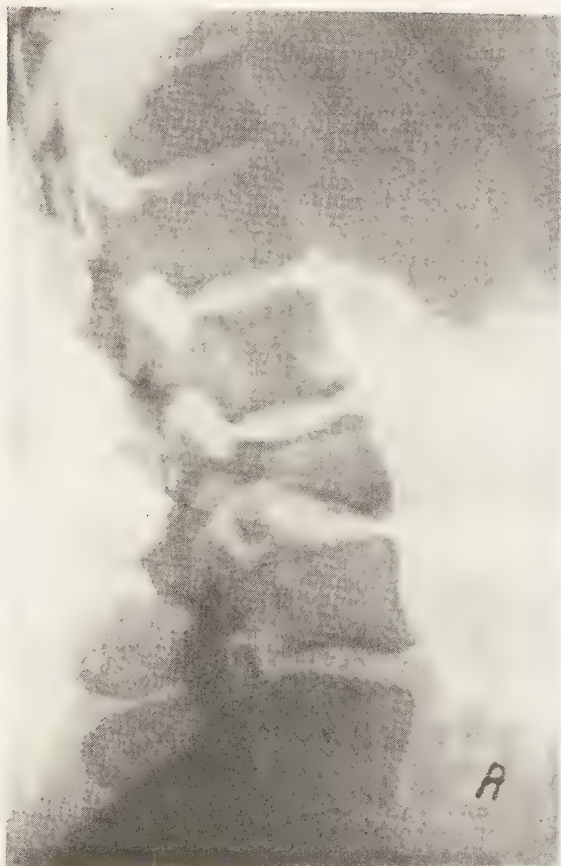


Fig. 1.

she fell backwards and immediately suffered from severe pain localized to the low back, without any tendency to radiate to the lower extremities. She was confined to bed for a few days, but since then she has suffered more or less constantly from a dull pain in the lumbar region.

In February 1954 a roentgenographic examination of the vertebral column was carried out, and of the pelvic bones, the thorax, and the right extremities as well. Pathological changes were found in the corpora of several vertebrae, in a number of the ribs, the ala oss. sacri sin. and in several of the proc. spinosi in the lumbar column. There was considerable compression of the body of L 2. The pathological changes consisted in small circular defects with a rather thick and well-defined outline. In the ribs these changes covered a considerable area, where the ribs at the same time were broader than usual and considerably expanded (see Figs. 1, 2). These changes were thought to be strongly suggestive of a dysplasia fibrosa ossium, and the patient was admitted to the Medical Department of the Landspítali Islands for further study.

Extensive changes were found on roentgenographic examination of the skull,

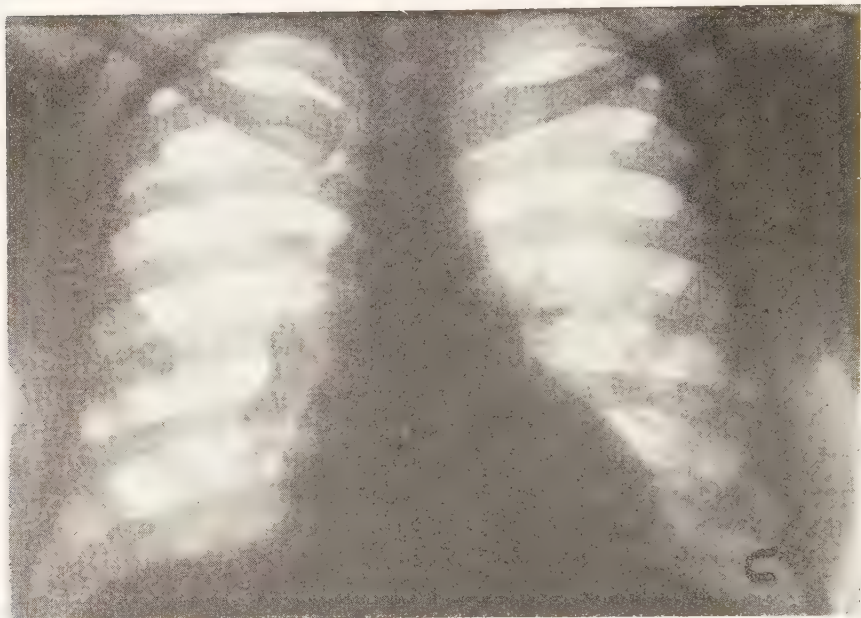


Fig. 2.

showing great expansion of the frontal bone, especially on the left side, great thickening of the base of the skull, the left os zygomaticum, and the orbital part of the left maxilla. An osseous mass was seen to protrude into the nasal cavity, dislocating the septum to the right. These thickenings did not seem to consist of compact bone, on the contrary, they seemed to be very loose in texture (see Figs. 3, 4). A postoperative defect was seen in the left os temporale. The left orbita was very much narrowed and seemed to be chiefly filled by a fibrous or osteoid mass.

The physical examination showed considerable prominence of the forehead on the left side forwards and lateralwards, corresponding to the os frontale, reaching down to the arcus of the os zygomaticum. There was some brownish pigmentation of the left upper eyelid, perhaps caused by the roentgen irradiation 1934. There was no edema of the right papilla, and the visual acuity was normal. Anophthalmus on the left side. Anosmia resp. hyposmia was found to persist. The neurological examination was normal, and excepting some tenderness of the lumbar region on palpation, the physical examination was otherwise normal on the whole.

Blood pressure was essentially normal, 140/80, the pulse rate 80.

The electrocardiogram was normal. The kidney function was normal as was intravenous pyelography. The blood urea was within normal limits, and the same was true of the basal metabolic rate. The sedimentation rate was 7 mm/1 h., hemoglobin 102 %, red cells 4.03 millions pr. mm³, white cells 3696 pr. mm³, and the differential count was normal. Sternal puncture gave normal results. The inorganic phosphorus content of the serum was 2.8 mg%, serum calcium 9.4 mg%, serum cholesterol 220 mg%, acid phosphatase 0.2, and alkaline phosphatase 6.7 Bodansky units. The excretion of calcium and phosphorus in the urine was within normal limits. The patient's height was 162.5 cm, the weight 68.8 kg. It should be pointed

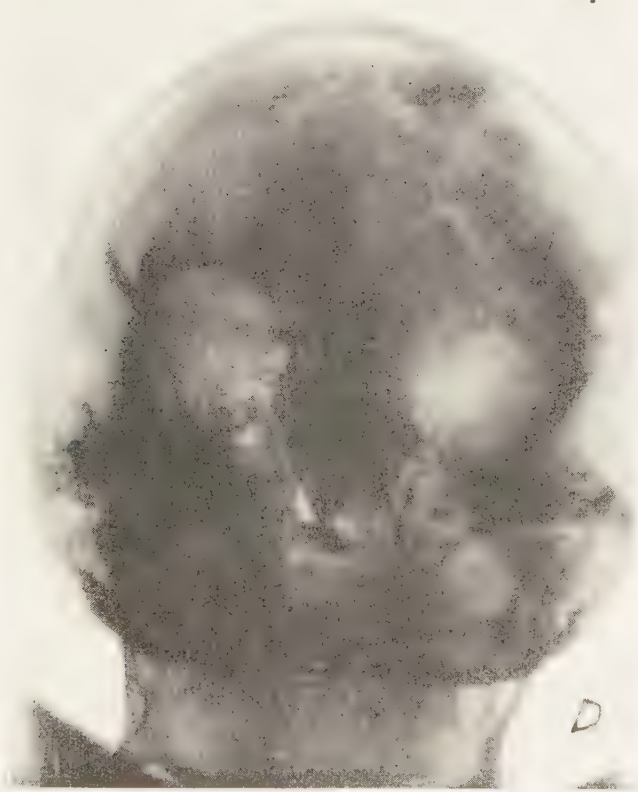


Fig. 3.

out that there was no history suggesting endocrine dysfunction at any time, and no abnormal pigmentation of the skin (left upper eye-lid?). The patient is highly intelligent.

One third of the left 11th rib was resected for biopsy. Macroscopically it was distinctly abnormal: it was broader than normal, with localized expansions. The cortex seemed to be perforated at many places, but no inflammatory reaction or signs suggesting a growth were visible. On cutting through the rib it was much softer than normal. The interior was composed of a light greyish-yellow mass, and no marrow could be seen.

A histological examination was performed by Dr. Ólafur Bjarnason, Department of Pathology, University of Iceland, who gave the following description of the pathological changes:

"A 5 cm long portion of a rib was submitted for examination. There was a slight localised expansion of the rib measuring in the greatest



Fig. 4.

diameters 2.1×0.9 cm. Cut section of this part of the rib showed light greyish-yellow, gritty tissue, with a few, pinhead-sized brownish dots scattered about. The cortex of the bone was very thin, measuring 1–2 mm.

Microscopic examination of sections from the expanded part showed no marrow, but instead of that a rather cellular fibrous tissue filled the spaces between trabeculae of poorly formed bone (Figs. 5 and 6). There was apparently widespread resorption of normal bone but also in places substitution of poorly formed, mainly osteoid, cancellous trabeculae (Fig. 6). In sections from the brownish dots seen macroscopically one could see clusters of hemosiderin-laden phagocytes in the fibrous tissue (Fig. 7).

The histological changes seemed to be fully compatible with the diagnosis of dysplasia fibrosa.

Specific inflammation, eosinophilic granuloma, lipoidosis, and malignant tumour formation could be ruled out.

The tissue was fixed in formol—saline and the sections stained with hematoxylin-eosin.”

The final diagnosis was thus dysplasia fibrosa ossium, based on the fact that other pathological conditions could be ruled out, that the roentgenographic findings were fairly suggestive, but first and fore-

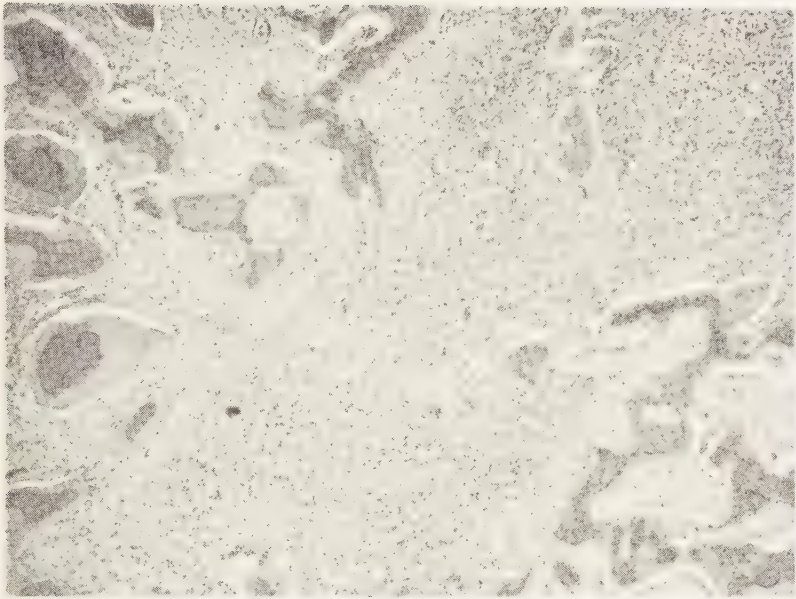


Fig. 5.

most on the microscopic picture of a bone lesion. The long history was also helpful.

This case is of considerable interest. The symptoms have been manifest for at least 20 years. In the beginning the pathological changes of the cranium were interpreted as a probable sarcoma, and later as a probable leontiasis ossea. The considerable protrusion of the left eye, which had developed in a relatively short span of time, suggested a tumour of the left orbita. Exophthalmus has been reported before. In a case, a boy aged 14 years, reported by *Albright* and associates, there was marked exophthalmus of the right eye and a dilated right pupil. In a child, this finding along with pathological roentgenographic changes in the skull—which may also have a “punched-out” appearance in dysplasia fibrosa ossium—may suggest the possibility of Hand-Schüller-Christian’s disease. Unilateral exophthalmus has also been reported by *Coley*.

As far as I know, bilateral papillary edema has not been reported before. This finding might suggest an intracranial growth, and make encephalography necessary. This was performed and found to be essentially normal at the Serafimer Lasarettet in the case reported here.

Coley saw a case in which the first symptom was deafness in the right ear, but closer examination showed involvement of the right side of the skull and several other places.

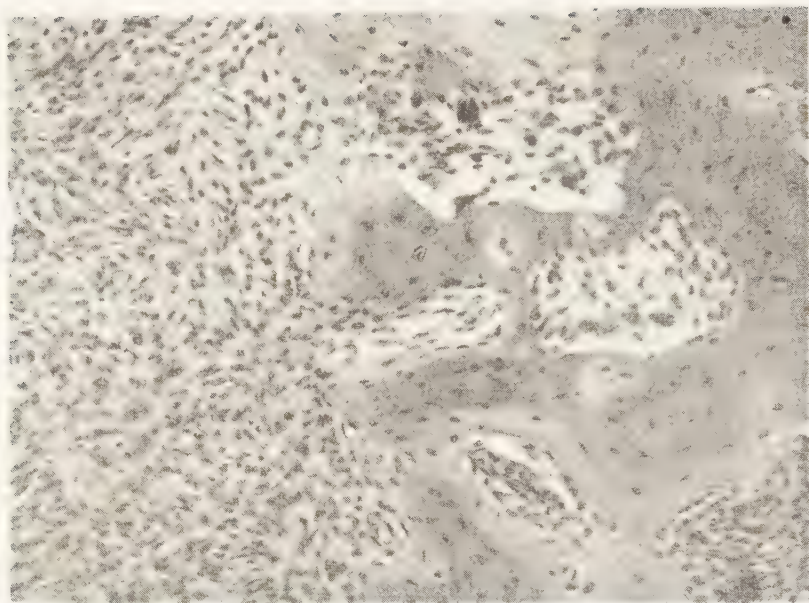


Fig. 6.

Anosmia resp. hyposmia was present in the case described here.

This disease may thus cause symptoms which are of considerable interest to neurologists and neurosurgeons, symptoms which may be present when there is severe involvement of the skull and the vertebral column.

SUMMARY

The symptoms, roentgenographic features, microscopic picture, diagnosis, and differential diagnosis of dysplasia fibrosa ossium are discussed. A personal case is reported, and attention is called to the possible neurological aspects of the disease in certain cases, with severe involvement of the skull and vertebral column. The prognosis is mostly good *quo ad vitam*, but the disease is often disabling when strategic parts of the skeletal system are seriously affected. There is no special treatment. Any treatment should be supportive and orthopedic in selected cases in which treatment is necessary. Systematic roentgenography should be performed in suspect cases, and microscopic examination of bioptic material is of great importance. Malignant transformation may occur. The etiology is obscure.

I wish to convey my thanks to *G. F. Petersen*, M.D., Head of the Roentgenological Department of the Landspítali islands, for kind permission to publish the roentgenograms.

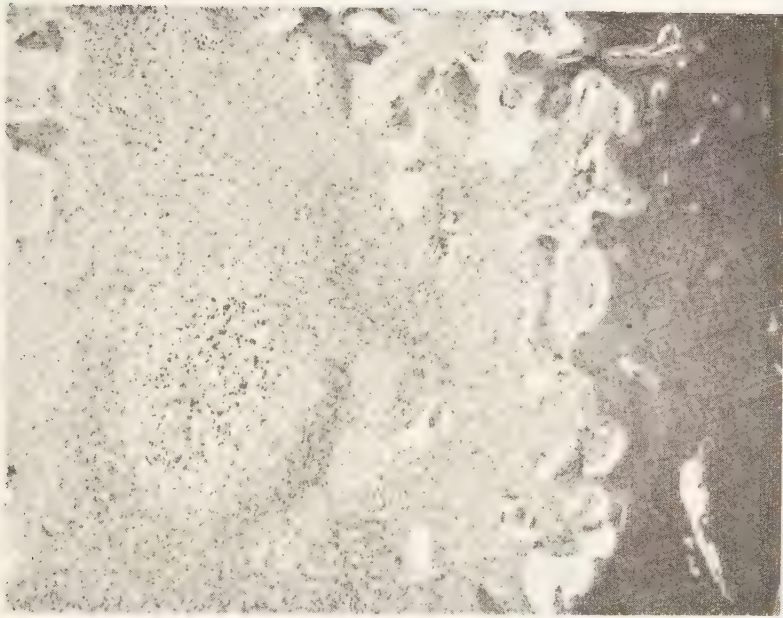


Fig. 7.

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DISSEMINATED SCLEROSIS

Influence of Age on the Different Modes of Progression¹

By

PAUL THYGESEN

The present study was designed exclusively to elucidate how and to what extent the patient's age at onset influences the subsequent course of the disease. Opinions differ in this respect. Several investigators (int. al. *Brain*; *Carter, Sciarra & Merritt*; *Friedman & Davidson*; *Lazarte*; *McAlpine*) have expressed the view that the course usually is more benign in patients of the older age groups. In contrast and with more statistical foundation—*Millar* as well as *Müller* found that patients whose symptoms appear before the age of 25 have a better prognosis than those with a later onset.

MATERIAL

Selection.

The material comprises patients admitted to the Neuromedical Department of the University Hospital, Copenhagen from June 1, 1947, to Dec. 31, 1948, whose disease was diagnosed after admission to hospital as disseminated sclerosis.

This particular section of the comprehensive material from the department was selected, because during the period in question a large number of sclerotics were submitted to anticoagulation therapy. Their histories were therefore obtained with particular thoroughness for purposes of therapeutic control.

The series is not absolutely representative of the disease, but more so than at any other time in the history of the department, and sufficiently representative for our present purposes.

¹ Aided by a grant from the P. Carl Petersen Foundation.

It comprises patients from the whole of Denmark, referred to the department in the usual way and, in addition, a number of out-patients with relatively mild illness referred for diagnosis and who were willing to undergo anticoagulation therapy. All the patients were admitted as in-patients while the treatment was being started. Lastly, the series was supplemented with sclerotics referred to us from the municipal departments of neurology in Copenhagen and Frederiksberg.

To be entirely representative of the disease the series presumably lacks a number of chronic cases, particularly of the older age groups.

Size and Composition.

Thus selected, the series comprises 171 patients, 104 females and 67 males.

The earliest onset was in a boy of 13 and the latest in a man aged 54. On admission in 1947-48 the average duration had been 8 years, ranging from a few weeks up to 32 years.

Age on admission:

	Females	Males	Total
Under 20 years	1	1	23
21-25 ..	13	8	
26-30 ..	11	8	46
31-35 ..	14	13	
36-40 ..	18	9	62
41-45 ..	25	10	
46-50 ..	7	7	40
51-55 ..	11	8	
Over 55 ..	4	3	

Ability on admission:

Wholly capable of working	36
Partially capable of working	47
Incapacitated, but able to manage simple duties	59
Incapacitated, unable to manage simple duties	29

The working capacity represents the resultant of the functional capacity of the four limbs, this classification paying no regard to the possible rôle of optic symptoms and mental disturbances. An ability test was made in the great majority of cases and used for the correction of the demands made by various occupations on man's limbs. More than half of the patients were housewives, and the sufficiency of an ordinary housewife in daily duties was used as the standard of functional capacity.

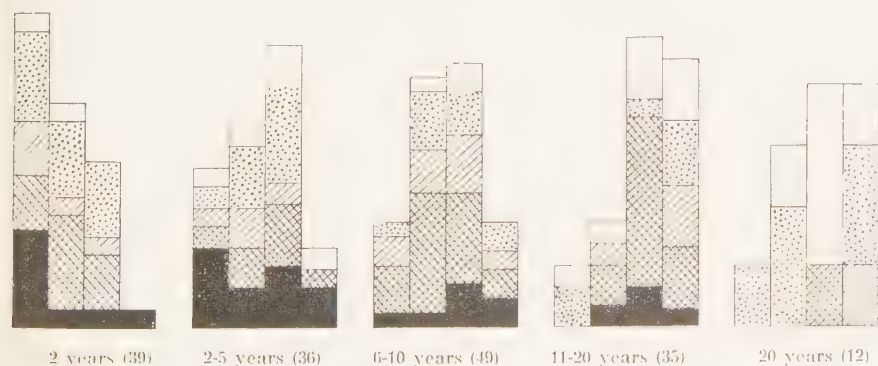
RESULTS

The first step was to study for each of the four ability groups the relation between the age at onset and the average duration until

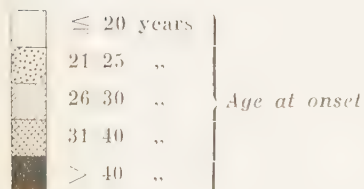
TABLE 1 and FIG. 1

Relation between age at onset, average duration until admission in 1947-48, and degree of disability at that time.

Age at onset	Total	Disability on admission in 1947-48			
		Wholly capable of working	Partially capable of working	Incapacitated, but able to manage simple duties	Incapacitated, unable to manage simple duties
<i>Under 25 years of age</i>					
Number	65	13	18	23	11
Average duration, years	9.4	6.9	8.4	9.0	14.6
Variation, years		26	25	32	18
<i>26-35 years</i>					
Number	53	10	18	15	10
Average duration, years	7.4	4.4	5.6	7.3	13.9
Variation, years		10	12	20	21
<i>Over 35 years</i>					
Number	53	13	11	21	8
Average duration, years	6.9	2.9	7.4	8.9	7.7
Variation, years		10	16	20	17
<i>Total cases</i>					
Number	171	36	47	59	29
Average duration, years	8.0	4.7	7.1	8.5	12.5



Duration of disease on admission in 1947-48



The 4 columns of each block represent the percentile distribution:

Column 1: Wholly capable of working.

Column 2: Partially capable of working.

Column 3: Incapacitated, but able to manage simple duties.

Column 4: Incapacitated, unable to manage simple duties.

admission in 1947-48 (which need not be tantamount to the time which the present degree of disability had taken to develop).

The figure illustrates how the disability increases with increasing duration and how the younger age groups gradually make up a relatively increasing proportion of the long-standing cases.

Within all three age groups in the table there are, after an average duration of 8 years, about equal numbers of patients who are wholly or partially capable of working on the one hand and of patients who are incapacitated on the other.

These values are not directly comparable with Müller's large series, *int. al.* because his definitions of various degrees of disability are different and more "pessimistic": "Moderate invalidity refers to a condition when the patient cannot move indoors without a stick, and when out of doors he needs two, also, and/or that he has difficulty in managing simple duties."

Despite the difference in grading of disability, there is probably a certain rough agreement with Müller's experience that "... ten years after the said outset about half the patients have become invalids." The distribution of disabled and non-disabled after an average duration of 8 years also corresponds quite well to the result of Allison's follow-up study. He found that the majority spent about half the total illness (in fatal cases an average of 19.5 years, among survivors 27.8 years) in a state of severe disablement.

The fact that the proportion of elderly patients decreases with increasing duration up to admission may be, at least in part, a result of the above-mentioned somewhat lop-sided representation of the disease in the present series. Several, particularly elderly and perhaps long-standing cases have probably not been admitted for treatment, partly because of lacking therapeutic optimism and partly because of certain misgivings in starting anticoagulation therapy for patients over 50 years of age. Furthermore, the excess mortality among the elderly patients must influence the present values for the surviving patients. Of the patients whose disease set in before the 25th year of age almost 10 per cent. should, according to Müller's calculations, have died within 8 years and about 20 per cent. if the disease had set in after that age. Kolb also found a significantly higher probability of dying among elderly patients.

Statistics substantiate the better average prognosis *quoad vitam* for young patients. Fig. 1 indicated that a relatively large number of young patients remain fairly capable of working despite long-standing disease. This indication is supported by the following special analysis of two extreme groups, viz. the fifteen patients whose disease set in before the age of 18 and fifteen who had reached the age of 45 at the time of

Status in 1947-48	First symptom manifested itself	
	before age of 18	after age of 45
Average duration	14.5 years	4.4 years
Wholly or partially capable of working	5 patients	6 patients
Incapacitated	10 „	9 „

the first manifestation (unless the first warning, perhaps in the form of a long past monosymptomatic attack, had been forgotten by the middle-aged patients).

Despite a duration three times longer than in the older groups, these young patients whose disease set in during childhood or adolescence, had not *as a group* become disabled to a greater extent than those who did not contract the disease until a ripe age.

A supplementary after-investigation, however, gives the surprise of showing that although the 15 young patients had in 1947-48 on an average been ill for $14\frac{1}{2}$ years, the 10 disabled ones had been disabled after an average duration of only $1\frac{1}{2}$ years. The corresponding period for the 9 old disabled patients was $3\frac{1}{2}$ years.

The same fact—so important in evaluating the prognosis for young patients—is illustrated in Table 1:

The variation in duration until admission in 1947-48 is twice as marked in the youngest group with an onset before 25 years of age as in the others. This applies practically speaking to all ability groups except the helpless chronic cases.

The variation is shown in details in Fig. 2.

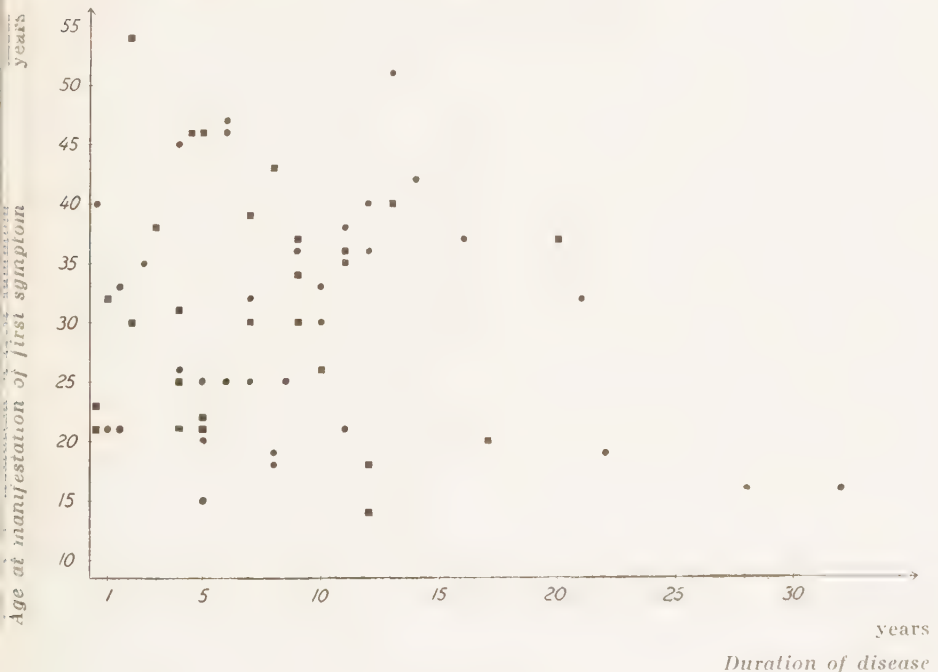


FIG. 2

Relation between age at manifestation of first symptom and duration in 59 cases (32 females and 27 males) who on admission in 1947-48 were incapacitated, but able to manage simple duties.

Fig. 2 shows that: In 23 instances the disease had set in before the 25th year of age and had at the time of admission lasted for an average of 9 years, ranging from a few weeks to 32 years. In 16 instances, i.e. more than two-thirds, the duration was below the average. Only 7 of this latter group raise the average duration up to 9 years by an exceptionally favourable course.

A comparison with the oldest age group—the 21 patients whose disease set in after 35 years of age—shows the average duration to be the same. But the variation is less marked, ranging from 6 months to 20 years, and these patients are equally grouped on both sides of their average duration of 8.9 years.

In spite of the small numbers involved or perhaps by virtue of the small numbers that permit a more detailed analysis, it is justifiable to maintain that the values in large statistics that report the most favourable prognosis in young sclerotics hide the important fact that a large proportion of the young patients are disabled in the course of a few years, more quickly than the total average of sclerotics.

The next question arising is whether the young patients are disabled by a course that differs in essence from that in older patients.

The results of analysing the course of a disease in retrospect cannot be but inaccurate. The current classifications into types of course often force one to violate the spontaneity and reality—or else our classifications are broken by incalculable variations in the course. Nevertheless, the disease often shows a tendency to choose a type of course from the very start and to follow this course in all essentials (12) although a continuous, intensive analysis of a short period (13) shows that a patient's successive *attacks* (the units of the disease at close range) seldom are of uniform type, not even in those cases in which *the type of course* (the disease in general retrospect) presents a certain constancy.

Despite this weakening of the types it will now be endeavoured to operate with three types of course, adapted to the following analysis of the way in which the 15 youngest and the 15 oldest patients reached the degree of disability which they displayed on admission in 1947-48.

(I) A type in which at least the predominant symptoms of the single attack are of acute, perhaps apoplectiform onset. As a rule, the attacks are indicative of a single or a few fresh lesions. The type is maintained as a unit regardless of the degree of disability caused, more or less temporarily, by the individual attacks. The characteristic feature is that the symptoms reach a climax within a few days or a few

weeks and that perceptible remission is obtained in the course of weeks or a few months. The cranial nerve symptoms and the sensory extremity symptoms predominate in many of these attacks which, however, also may consist in e.g. a severe, but usually only temporarily disabling mono- or hemiparesis of an apoplectiform onset.

(II) A rather heterogeneous type, characterized by increasing disablement due to successive spread of more and more lesions and without a tendency to remission, at least socially significant remissions, of the symptoms *as a whole*. (In a close-up study the single "progressive" attacks usually represent a real accumulation of single symptoms developing fairly simultaneously or more successively. Such a progressive attack usually consists of intensification of existing symptoms — recurrence of previously remitted symptoms — symptoms indicating dissemination within the central nervous system). At the end of a few years, the disability of such patients is usually caused mainly by incoordinative extremity symptoms.

(III) A type in which it is difficult to correlate a steadily increasing disability with well-defined, successive outbursts of new symptoms and intensification of existing symptoms occurring in attacks. It is this type of gradual deterioration during a slow downhill course which is difficult to record in a close-up study embracing a given, limited period. *Putnam*, *int. al.*, was apt to evaluate this type as a sign of secondary mesodermal fibrosis in the old, large, intense lesions of disseminated sclerosis. At all events: In retrospect, the type is characterized by the absence of any tendency to remission, at any rate of the predominant symptoms—symptoms which usually suggest lesions of the pyramidal tracts. It is this type of sclerosis which mostly makes us resort to diagnostic myelography.

Whenever the types of course showed a tendency to succeed each other (in 7 of the 30 patients and usually from type I→II), the case was classified according to the type that had prevailed during the greater part of the disease.

About two thirds of both age groups had become disabled at the time of examination, 14.5 and 4.4 years, respectively, after the onset before the 18th and after the 45th year of age.

(I) The acute, intermittent course prevailing in young patients had only disabled 2, although 9 of the 10 patients had had symptoms from the cranial nerves as well as from the upper and lower limbs at one or usually more stages of the disease. The 8 patients of this group who were capable of working had remained so despite an average duration of about 10 years. In the remaining 2 cases, this type of course had required up to 20 years before disabling the victims.

TABLE 2

Retrospective course in the 30 patients whose symptoms set in before the 18th year of age (15) and after the 45th year (15).

Retrospective course	First symptom before age 18		First symptom after age 45	
	Wholly or partially capable of working	Incapacitated	Wholly or partially capable of working	Incapacitated
(I) <i>Predominantly</i> acute intermittent with complete or partial remissions	5	2	3	0
(II) <i>Predominantly</i> progressive, characterized by dissemination	0	4	0	3
(III) <i>Predominantly</i> progressive, perhaps stationary, <i>dominated</i> by intensification of relatively few symptoms	0	4	3	6

(II) The progressive, disseminating type in which each outburst may be likened to the firing of a shotgun, disables all the patients and does so rapidly, viz. within an average of 3-4 years, whether the disease sets in before 18 or after 45 years of age. All 7 patients exhibited symptoms and signs from cranial nerves and from the upper and lower limbs as well as sphincter disturbances in the course of just a few years. All had symptoms from the pyramidal tracts, but in at least 6 of the 7 cases the disabled condition was predominated by incoordinative extremity symptoms and postural instability.

(III) The slowly progressive, "tough", mainly spinal type prevailing within the oldest group appears to disable the patient in the course of 4-6 years. All cases are predominated by pyramidal tract symptoms in the form of spastic paraparesis and sphincter disturbances, although only 3 of the 13 patients escaped more or less remittent symptoms from the cranial nerves and upper limbs in the course of the average duration of 7½ years until admission in 1947-48.

It is evident that the values in Table 2 cannot stand alone. They represent the analysis of a detail and must therefore be viewed in the light of the study as a whole and previous studies (12, 13). The relevance of these values is supported by the following examples (cf. Table 1).

Among the 31 patients whose disease had set in before 25 years of age and who at the time of examination in 1947-48 were wholly or partially capable of working in their original occupation, the duration was over 10 (up to 26) years in 10. In at least 8 of the latter the disease appeared in retrospect as a typically intermittent

type predominated by mono- or oligosymptomatic attacks, constantly followed by rapid and often complete remission.

Twelve patients whose first symptom was manifest before 25 years of age were incapacitated (and some of them unable to manage simple duties) in 1947-48 despite a duration of less than 5 years. In 3 or 4 of the patients, the present degree of disability had to be interpreted as a transient phenomenon, due to an acute attack, with good chances of remission during a continued observation. In 6 cases the disability was permanent, the result of a progressive disseminating course.

Lastly, it must be stated that a comparison of the course and the prognostic average values for females and males revealed no essential differences. Particularly, there was no special tendency towards accelerated disease activity or alteration of the course on the whole in the 52 females who were over 40 years of age on admission in 1947-48. (Nine were wholly and 13 partially capable of working as housewives, 30 were practically incapacitated and of them 13 were unable to manage simple duties). In other words, there is no evidence to support *Stoltzenberg's* assumption that the hormonal disturbances of the menopause should exert an unfavourable influence on the course.

CONCLUSIONS AND SUMMARY

A total of 171 patients, approximately representative of the different types of course and stages of disseminated sclerosis, were examined after having been affected with their disease for an average of 8 years.

Calculation of the average values shows that those who contract the disease at an early age retain their working capacity longest. This accords with the results from more comprehensive statistics which, however, fail to disclose the fact that a large proportion—perhaps half—of the young patients are disabled in the course of only a few years more rapidly than an average section of sclerotics. While giving its young victim the greatest chance of a particularly favourable prognosis, the disease is at the same time most dangerous to the young sclerotic.

The great chance for the young patient is the acute, intermittent type of course which often remains inactive for years and which often does not start disabling until it has lasted for 10-20 years and perhaps never.

The great risk for the young patient is a progressive, disseminating course, with or without a tendency to remission of single symptoms, disabling in the course of only a few years, primarily by incoordinative extremity symptoms.

When setting in at a more advanced age, the disease is more predestined for a slower downhill course, in retrospect characterized by more or less steadily intensifying pyramidal tract symptoms.

With reference to previous studies, it is pointed out that the different modes of progression are essentially too closely related and too far from being individual specific to motivate the assumption of fundamental differences. The demonstrated tendencies indicate, however, that the reaction of the constitution to established disease (the defence mechanism of the patient) varies to some extent according to the age at onset.

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CEREBRAL CHANGES IN CERTAIN PRESENILE AND SENILE PSYCHOSES

By

G. VRAA-JENSEN

In recent years, there has naturally been an increased interest in the diseases of aging, also within the domain of brain diseases. Some features of the neuropathological problems relating to the most important of these brain diseases, viz. presenile and senile psychoses, will be outlined below.

The first presenile psychosis to be distinguished as a nosological entity was Pick's disease described in broad outline by *Pick* in 1892. Its histology was not described in detail until 1911 (*Alzheimer*).

The neuropathological appearances are somewhat varied. In the gross, localized atrophies of the cortex are typical, but their situation varies: as a rule, they affect the frontal and temporal lobes, but nearly always the anterior portion of the insular cortex as well. The brain as a whole usually shows slight, sometimes more advanced, general atrophy, often predominating in one hemisphere. Most frequently, the circumscribed atrophies set in at special sites, the so-called "Schrumpfungscentra", from where they spread to the surrounding cerebral cortex. Such "Schrumpfungscentra" are present partly in the frontal lobes at the gyri recti and partly in the polar regions of the temporal lobes. From the temporal poles the atrophic process may spread to the 2nd, 3rd, and 4th temporal gyrus, whereas the posterior and central part of the 1st gyrus, containing Wernicke's sensory speech centre and the cortical auditory centre, are seldom involved. Furthermore, microscopical examination has revealed a special "Schrumpfungscentrum" in Sommer's sector in the hippocampus.

Microscopically, the most marked changes are often encountered in the superficial layers of the atrophic cerebral cortex (I-III a), partly in the form of ballooned nerve cells with argentophil *cytoplasmic granules* and excentric nuclei and partly in the form of small, sclerotic nerve cells. Moreover, there will be some cortical gliosis, degeneration

of axis cylinders, and reactive proliferation of glia fibres in the white matter. In the glia cells *von Braunnühl* and *Leonhard* (1934) found a siderophil substance.

Sometimes, however, the changes of the nerve cells are slight or non-specific, focal subcortical gliosis being the most outstanding feature. On the basis of this difference in pathological appearance, *Neumann* (1949) tried to divide Pick's syndrome into two groups. There is, however, no clinical evidence that this pathological classification represents separate disease entities.

Pick's disease may also involve the basal ganglia. The changes of the corpus striatum mainly affect the caudate nucleus and those parts of the putamen and globus pallidus which are adjacent to the internal capsule. *von Bagh* (1946) has compared the pathological findings in the corpus striatum to some cases of Huntington's chorea. According to *von Bagh* the changes are of the same type, there being in both lesions degeneration of nerve cells as well as myelinated fibres combined with glial proliferation. Only the spread of the morbid processes differs, Huntington's chorea involving all segments of the corpus striatum. *Simma* (1952) has also compared the anatomical appearances in Pick's disease and Huntington's chorea. He reports that the pathological processes in the two diseases differ in essential respects, the centrum medianum of the thalamus often showing coarse retrograde cell changes in response to the process in the corpus striatum in Pick's disease, but not in Huntington's chorea. In the latter there may at the utmost be some glial proliferation, possibly owing to trans-neuronal atrophy. In addition, the entire parenchyma of the corpus striatum is involved by Pick's disease, whereas in Huntington's chorea it is almost purely a case of cellular degeneration.

In Pick's disease, moreover, there may be severe changes of the substantia nigra, and the hypothalamus is occasionally involved. As far as the tracts are concerned, it is remarkable that the fronto-pontine tracts are oftener affected than the temporo-pontine ones; in exceptional cases the pyramidal tracts are involved, too.

There has been much doubt regarding the aetiology of Pick's disease. *Pick* himself believed that it was to be interpreted as a variety of senile dementia, but this view has now been generally abandoned. The possibility of an arteriosclerotic basis has been suggested, but this has been opposed by *Onari* and *Spatz* (1926), who contend that most cases exhibit little atherosclerosis and that the spread of the morbid lesions does not show any dependence upon the vessels. *Ferraro* and *Jervis*, in 1936, advanced the theory that angiospasm were of pathogenetic significance, but have later (1940) abandoned this theory and

set up the hypothesis which has gradually been accepted by most workers, viz. that the condition is a heredo-degenerative disease *sui generis*. It is parallelized with Huntington's chorea and certain cerebellar atrophies which also occur during the presenium. Recent genetic studies have supported this view.

Unlike Pick's disease, Alzheimer's disease is characterized grossly by diffuse atrophy of the cerebral cortex and microscopically by the occurrence of senile plaques and by special changes of the cells and neurofibrils. There is, moreover, a varying degree of degeneration of the cortical cells, especially in the superficial and middle layers. In the basal ganglia there is also breakdown of nerve cells accompanied by gliosis, and at times the mesencephalon, particularly the substantia nigra, is altered. The pathological lesions are on the whole more diffuse than in Pick's disease (*Lindgren, 1952*).

Both the senile plaques and Alzheimer's cells were observed by *Alzheimer* (1911), who described the senile plaques or "Drusen" as being made up of a nucleus formed by the deposition of pathological metabolic products. This nucleus is surrounded by the so-called "Drusen-hofe" showing a number of changes which *Alzheimer* interpreted as reactive phenomena in the nervous tissue surrounding the nucleus.

A particularly thorough study of the nature of senile plaques was published by *Soniat* (1941), who examined 100 brains containing senile plaques. He describes the plaques as small, spherical bodies scattered in the cerebral cortex. They are not uniform in structure and vary in size, being usually 10-150 microns in diameter. These bodies are most numerous in the cortex of the frontal lobes and in the hippocampus, especially in the deep cortical layers. Senile plaques usually coexist with diffuse degeneration of the nerve cells which often contain lipofuscin. Various impregnation methods very often show a degenerated nerve cell in a plaque, sometimes in its centre and sometimes of a peripheral location. In some instances, the nucleus and nucleolus are the only remnants of the nerve cell that can be identified in the plaque. In other cases, the plaque consists of a homogeneous or slightly granular central area surrounded by radially arranged argyrophil structures.

In the plaques and especially in their immediate neighbourhood there are also glia cells of which microglia cells—frequently hypertrophic—are commonest. Fibrillar astrocytes are not uncommon. Their fibrils either penetrate the plaques or form a capsule around them. Oligodendrocytes, on the other hand, are few and often degenerated.—The neurites present in or immediately outside a plaque are extremely

argyrophil. As a rule, they are fragmented; some of the fragments are granular and others swollen, usually ending in club shape.

The other typical feature of Alzheimer's disease, the Alzheimer cells, occur in up to 75 % of the cases that show senile plaques in the brain. The characteristic of Alzheimer cells is thickening and fusion of the intracellular neurofibrils, which show a tendency to form whorls. As the degenerative process advances, the contours of the cytoplasm as well as the nucleus become blurred, the neurofibrils being left as the only remnants of the nerve cells. Such remnants of nerve cells are often present in various forms in the plaques.

It is not yet clear what histochemical processes lead to this special form of nerve-cell degeneration, although certain findings indicate that Alzheimer changes are due to dehydration. This view has been supported by experiments performed by *Stern* and *Elliott* (1949), who injected a 25 % solution of glucose into rabbits. Subsequent examination of the brains disclosed changes of the ganglion cells which resembled the initial stage of Alzheimer degeneration, irregularly distributed to all parts of the brain. In commenting on their experiments, *Stern* and *Elliott* call attention to *Cajal's* and *Tello's* investigations of hibernating reptiles, which showed that the morphology of the intracellular neurofibrils is not constant, but varying with extracerebral factors, such as fluctuations in temperature and water metabolism. Although dehydration is thus indubitably a factor in the development of Alzheimer's cells, *Stern* and *Elliott* stress that other factors unknown at present presumably also play a role. If not, there would be no explanation why Alzheimer's cells have a predilection for phylogenetically recent areas of the brain.

There has been much discussion as to whether Alzheimer's cells exerted any influence on the development of the senile plaques.—*Creutzfeldt & Metz* (1926) and *Struwe* (1929) do not think so, claiming that no cells—be it ganglion cells or glia cells,—play any genetic role in this respect. In contrast, *Ferraro* (1931) found that senile plaques might well be formed on the basis of degenerated nerve cells, but that microglia cells were more frequently the primary point of origin. Similarly, *Boumann* (1934) on the basis of his investigations concluded that degeneration of nervous tissue was a *sine qua non* for plaque formation. *Gellerstedt* (1933) found signs that plaque formation was dependent upon vascular changes, directly or indirectly through nutritional disturbances. In *Goodman's* (1953) opinion Alzheimer's neurofibrillar degeneration as well as plaque formation are caused by disturbances of the cerebral iron metabolism with secondary devitalization.

In the above-mentioned thorough study on the senile plaques, *Soniat* maintains that in the great majority of cases a senile plaque develops from degenerated nerve cells, and as a rule the degenerative process consists in typical Alzheimer changes. The breakdown products attract microglia cells which in the attempt at phagocytizing these breakdown products become involved in the plaque formation. According to *Soniat*, oligodendroglia more accidentally become part of a plaque, whereas astrocytes convene as they do wherever nervous tissue is breaking down.

Another aspect which has been the subject of much discussion is the nature of the substances typical of the plaques. *Divry* (1927) claimed that they were identical with amyloid, and this has been confirmed by *Krücke* (1950) and *Hechst* (1929). *Hechst* also found that a lipid substance might occur in combination with the amyloid. *Missmahl & Hartwig* (1954), in polarization studies, interpreted the senile plaques as a sign of paramyloidosis. *Dias* (1930), however, could not find the double refraction so characteristic of amyloidosis in any classic plaque, unless the brain had been fixed in formol for a long time. His studies on the whole indicate that the double-refractive substance which many authors have described as a characteristic of the plaques, is a fixation phenomenon and not specific of the senile process. In this connection it must be mentioned that in a case with numerous senile plaques examined by *Reiss & Staemmler* (1950), all amyloid reactions were negative. Thus, the chemical nature of the plaques remains unelucidated, but the investigations published to date indicate that histochemically the plaques may vary within rather wide limits.

In classifying Alzheimer's disease etiologically and pathogenetically, it must be borne in mind that the structures which characterize it have been found also in brains from persons with senile dementia as well as from old persons without any definite psychic abnormality (*Struwe*, 1929; *Gellerstedt*, 1933). In contradistinction to Pick's disease which is usually interpreted as a disease *sui generis*, Alzheimer's disease appears to be closely related to senile dementia, although constitutional and perhaps also inherited factors are contributory. In *Jervis'* (1945) opinion, certain exogenous factors of a toxic or infectious nature may also be of pathogenetic significance.

Although pathologically alike in e.g. seldom showing atherosclerotic changes in the brain, Pick's disease and Alzheimer's disease differ in fundamental respects. As mentioned above, the main difference is that in Pick's disease the atrophy of the cerebral cortex is localized, whereas in Alzheimer's disease it is diffuse. In addition, the neurofibrillar, intracellular changes as well as the argentophile plaques occur practi-

ally speaking only in Alzheimer's disease, which, on the other hand, never exhibits the ballooned cells which are almost invariably present in Pick's disease.

While Pick's disease and Alzheimer's disease predominate in the group of presenile psychoses, senile dementia and arteriosclerotic psychoses are the most outstanding psychic abnormalities in the senium.

As already mentioned, the pathological findings are the same in senile dementia and in Alzheimer's disease. In silver-impregnated preparations, senile plaques and Alzheimer's cells predominate the histological picture. These structures occur particularly in the superficial cortical layers. Sections stained by the method of Nissl show changes of the nerve cells which are partly of a non-specific nature. Thus, shrinkage and atrophy of the nerve cells is very common. Some cells are very pale, chromophobe, while others are dark, shrivelled, and sclerotic. Deposits of lipid are frequently present in the nerve cells, usually in the form of acid-fast lipofuscin. Some neurons may be chromatolytic. As a rule, the cortical architecture is fairly well-preserved, although many nerve cells have perished. Generally, there is severe microglia reaction, and immediately below the cortical surface typical proliferation of astrocytes (marginal gliosis). As in Alzheimer's disease, the changes are most outstanding in the frontal lobes, especially in the polar regions, whereas the occipital lobes are least affected. There are, in addition, degenerative nerve cells changes with glial proliferation in the basal ganglia, the thalamus—particularly the centrum medianum (*Simma, 1949*)—the substantia nigra, and the grey matter around the third ventricle and the aqueduct of Sylvius. In the cerebellum, there will be breakdown of a few Purkinje cells, but otherwise the cells of the cerebellum and the brain stem usually show little change. As far as senile plaques are concerned, there are often several in the amygdaloid nucleus, somewhat fewer in the caudate nucleus and in the putamen. In the white matter dilatation of the perivascular spaces is a common sign and so is deposition of calcium in the vessel walls, particularly in the basal ganglia. On the whole, about half the cases of senile dementia are complicated by vascular changes, of course primarily arteriosclerosis (*Rothschild, 1945*). In most cases, however, these vascular changes do not predominate the total pathological appearances in senile dementia, although there may be such mixed cases in which it is difficult to decide which changes represent senile dementia and which arteriosclerosis.

Just as there are pathological appearances which are characteristic of senile dementia, there are pathological changes which are due almost

exclusively to cerebral arteriosclerosis and which are therefore typical findings in arteriosclerotic psychoses.

What is called by a collective term cerebral arteriosclerosis is in fact a motley picture of different pathological structures which may be isolated or combined. The arteriosclerotic changes that may occur in the brain are atherosclerosis, arteriolosclerosis, arteriocapillary fibrosis, and in rare cases Mönckeberg's calcification of the tunica media.

Atherosclerosis primarily affects the large cerebral arteries which show yellow and grey plaques distributed irregularly in the vessel walls that are thickened and hard with resulting constriction of the lumen. The pathological process is primarily degeneration of the intima which exhibits infiltration with lipids. Subsequently, there will be various reactive phenomena consisting in degeneration of the elastic tissue, proliferation of connective tissue—particularly in the intima and media—and later deposition of calcium.

Arteriolosclerosis consists in hyalinization of the wall of the small arteries and precapillaries. The hyaline substance frequently undergoes fatty degeneration with subsequent destruction of the vessel wall. In some instances, however, the intima remains intact, being at the utmost somewhat swollen. Constriction or complete obliteration of the lumen completes the picture.

Arteriocapillary fibrosis is usually combined with atherosclerosis and arteriolosclerosis, although it may occur isolated. The capillaries, and perhaps also the somewhat larger vessels of the outer cortical layers and of the white matter become surrounded by a gradually ever denser meshwork of argyrophile fibrils. Gradually, the meshwork constricts the lumen of the vessels involved and consequently compromises the circulation.

Lastly, calcification of the media may be encountered in the basal ganglia in rare cases. This vascular disorder, however, is by no means of the same importance in the cerebral vessels as in the big arteries of the limbs.

Some of the changes caused by the arteriosclerotic lesions in the cerebral tissue may be seen with the naked eye as areas of hæmorrhage or malacia.

Besides these changes, called "complete destruction", small foci with "incomplete destruction" are important features in the histology of cerebral arteriosclerosis. Incomplete destruction may be of the most varied forms. The commonest type is Alzheimer's cortical "Verödungen" characterized by the loss of nerve cells within localized areas of the cortex. As a rule, this lesion is not accompanied by a breakdown of other nervous tissues or by reactive phenomena worth mentioning on the part of the glia or blood vessels.

Often, especially within the area of the basal ganglia, there is marked dilatation of the perivascular spaces, at times so marked as to amount to "état criblé". Frequently, there is also perivascular gliosis. Finally, the so-called "Erbleichungen" are common phenomena; these are small and scattered foci of partial or complete demyelination in the white matter.

In addition to the focal changes, deposition of lipofuscin in several nerve cells is not an uncommon phenomenon in cerebral arteriosclerosis. Sometimes, there is also diffuse proliferation of astrocytes in the white matter and even proliferation of astrocytes in the superficial cortical layer, viz. marginal gliosis.

It will be seen that the histological picture of cerebral arteriosclerosis is a rather motley one. Attempts at correlating the anatomical substratum with the clinical manifestations of arteriosclerotic psychoses have also failed, except in respect to the coarsest changes.

Although the presenile and senile psychoses under discussion differ from most other psychic disorders in being associated with outstanding pathological changes and although the severity of the psychic symptoms generally corresponds to the spread and intensity of the organic changes in the brain (*Hoff & Seitelberger, 1953*), it has proved extremely difficult to demonstrate a relationship between structural changes and given morbid features of the psychic condition.

As early as 1911 *Alzheimer* realized that the senile plaques did not give rise to any given, classifiable psychosis, and this has been confirmed by subsequent research. *Spatz (1937)*, studying *Pick's disease* and other focal lesions in the basal cerebral cortex, claimed that he had found evidence that pathological changes in this area of the brain are of more significance to the "höchsten seelischen Leistungen" than previously believed. He admits, however, that in this important respect, we "noch ganz am Anfang der Erkenntnis stehen."

At our present stage of knowledge, we can hardly get any further than presuming like *Newton (1948)* that the mental changes are caused by the breakdown of nerve cells and that this breakdown is related to primary, hereditary properties of the nerve cells or to secondary changes caused by vascular or other factors unknown at present.

Thus, a number of important problems within the neuropathology of presenile and senile psychoses are still awaiting their solution.

SUMMARY

The neuropathological findings in Pick's disease, Alzheimer's disease, senile dementia, and arteriosclerotic psychosis are reviewed.

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SPASME DE L'ŒSOPHAGE DANS LE SYNDROME DE WALLENBERG

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Il est bien établi que parmi les symptômes qui constituent le syndrome de Wallenberg, les troubles de la déglutition sont dominants; à côté de ceux-ci on observe vertiges, dysarthrie, troubles croisés de la sensibilité à douleur et à la température, et troubles homolatéraux oculo-pupillaires. Lewis et collab. jugent la fréquence de la dysphagie à 80 p.c., ce qui correspond à mes observations, comprenant env. 40 cas.

La dysphagie est généralement modérée; les aliments s'engagent dans le nasopharynx ou dans la glotte, ou bien le bol alimentaire s'arrête au niveau de l'hypopharynx. Dans certains cas, la déglutition devient impossible et l'alimentation par sonde gastrique s'impose. Enfin, il existe des cas isolés dans lesquels une sonde même n'a pû être passée par suite d'un spasme de l'oesophage.

L'existence de ce spasme oesophagien, provoqué par une parésie monolatérale des muscles de la déglutition, a entraîné des discussions dans la littérature et conduit à diverses délibérations d'ordre physiologique.

En fait les avis sont partagés sur les données mêmes de l'innervation normale du pharynx et de l'oesophage.

Dans une communication antérieure, nous avons rendu compte d'un cas du syndrome de Wallenberg (s. de W.), présentant une parésie spasmodique de l'oesophage¹. Ici nous allons faire une analyse plus approfondie de cette question, en nous basant sur trois observations de troubles graves de la déglutition.

¹ J. C. Nielsen & Knud Winther: Soc. dan. de neurologie le 26 oct. 1949 et Soc. dan. d'otologie le 1 nov. 1950, - cas 3 du présent travail.

Obs. 1. Homme, âgé de 65 ans. Antérieurement bien portant. Le 26 octobre 1953 il apparaît une hémiparésie légère passagère. Le 23 novembre il éprouve subitement un trouble de la déglutition, ne pouvant rien avaler. A part cela, seulement des vertiges et des paresthésies de l'hémiface gauche. Le malade fut admis dans un hôpital de province. La dysphagie étant tenace, on pratiqua l'alimentation artificielle par sonde gastrique.

A l'admission, trois semaines plus tard, à l'Hôpital départemental de Copenhague, serv. F, (j. no. 232/54), les troubles cités persistaient.

L'examen mit en évidence:

- syndrome de Horner à gauche,
- diminution du réflexe cornéen g.,
- hypoesthésie à la douleur et à la température de l'hémiface g. et des membres d.,
- parésie de l'hémivoile g., voix bitonale,
- anesthésie de l'hypopharynx,
- nystagmus horizontal-rotatoire vers g.,
- signe de Babinski d.,
- ataxie des membres g.

On maintint la sonde gastrique jusqu'au 23 décembre, la déglutition étant alors devenue possible.

Il s'agit d'un cas typique du syndrome de Wallenberg, dominé par l'impossibilité de déglutition; seul l'examen approfondi révèle les symptômes significatifs, parmi lesquels il faut noter l'anesthésie de l'hypopharynx.

Obs. 2. Homme, âgé de 72 ans, admis à l'Hôpital municipal de Copenhague, serv. otol., le 28 avril 1930, pour troubles de déglutition, apparus subitement un mois avant, avec vomissements, dysarthrie légère et paresthésies brûlantes au niveau du bras g.

L'examen montre:

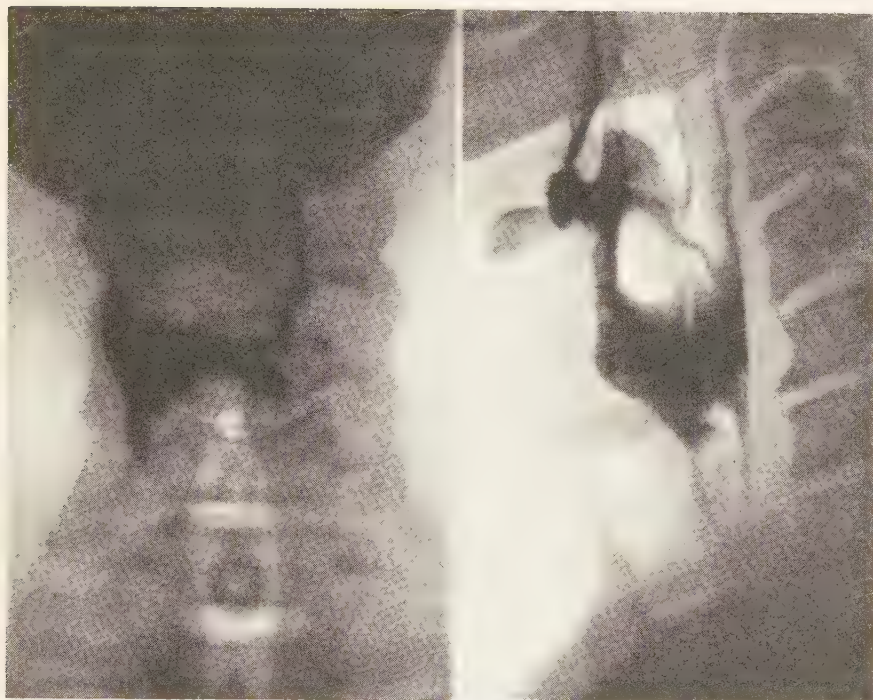
- syndrome de Horner d.,
- hypoesthésie de la cornée d.,
- parésie de l'hémivoile d. avec signe de rideau,
- hypoesthésie du bras g.,
- signe de Babinski g.

La parole était normale.

La radiographie de l'oesophage montra un arrêt de la matière de contraste au niveau de la bouche de l'oesophage. Aucun signe tumoral.

Ici aussi il s'agit d'un cas typique du s. de W. avec une dysphagie grave, dominant le tableau morbide et démontrée radiographiquement.

Obs. 3. Homme, âgé de 50 ans, toujours bien portant, avouant un éthylysme important, admis à l'Hôpital dép. de Copenhague, serv. otol. (j. no. 297/48) le 7 février 1948 pour troubles de la déglutition, apparus au réveil trois jours avant. Le malade ne pouvait rien avaler, ni liquides, ni solides. Autrement: dysarthrie légère et paresthésies de l'hémiface d.



Cas. 3.

Radiographie montrant l'arrêt de la substance de contraste au niveau de la bouche de l'oesophage (15 min. p. c.).

L'examen mit en évidence:

- miosis d.,
- parésie légère de l'hémivoile d.,
- nystagmus diagonal (derrière les lunettes de Bartels).

A part cela, rien d'apparent.

La radiographie de l'oesophage révéla un arrêt complet de la matière de contraste au niveau de l'orifice supérieur de l'oesophage.

A l'oesophagoscopie, on rencontra une fermeture spasmodique circulaire, impossible à forcer, ne s'ouvrant même pas après anesthésie ultérieure par pantocaine. Une bougie no. 20 rencontra aussi un obstacle. Le traitement par médicaments spasmolytiques resta inefficace.

L'état laissant soupçonner une affection bulbaire, on demanda une assistance neurologique.

A l'examen le 14 février nous avons constaté:

- syndr. de Horner complet du côté d.,
- anesthésie cornéenne d.,
- hypoesthésie de l'hémiface d.,
- nystagmus vertical-diagonal,
- parésie douteuse de l'hémivoile d.,
- dysarthrie légère,

- hypoesthésie à la température aux membres g. et à l'hémitronc g.,
- signe de Babinski g.

Le diagnostic fut posé d'un s. de W.

L'impossibilité totale de déglutition nécessita d'abord l'introduction d'une sonde duodénale, puis une gastrostomie (le 5 mars, serv. chir. D.). Des essais répétés de dilatation de l'orifice de l'oesophage ne donnèrent pas de résultat.

Grâce à l'alimentation artificielle par la gastrostomie, l'état du malade s'améliora.

11 mois après le début de la maladie, la déglutition redevint subitement possible, d'abord pour des liquides, puis pour des solides bien mâchés.

Une radiographie de l'oesophage un mois plus tard montra un passage libre; il n'y avait plus qu'une rétention négligeable au niveau de l'hypopharynx.

Le malade ayant regagné son poids d'autrefois, une fermeture de la gastrostomie fut impossible. Au cours d'un examen au mois d'octobre 1949, il se plaint seulement des paresthésies à l'hémiface d., et des douleurs des membres et de l'hémitronc g. Objectivement: syndrome de Horner d., hypoesthésie cornéenne d., hypoesthésie croisée, parésie légère de l'hémivoile d. et signe de Babinski g.

En 1952, enfin, la gastrostomie fut fermée. La radiographie montre un passage libre à l'oesophage.

Il s'agit dans ce cas, très démonstratif, d'un s. de W., dominé complètement par l'impossibilité totale de déglutition à la suite d'un spasme de la bouche de l'oesophage, démontré radiographiquement. Une gastrostomie s'imposa. Le spasme persista pendant 11 mois.

Dans les trois observations, citées ici, nous sommes en présence d'un syndrome de Wallenberg avec troubles massifs de la déglutition, initiaux et dominants dans l'aspect clinique.

Tandis que la dysphagie légère, si fréquente dans le s. de W., s'explique par une parésie de l'hémivoile (engagement des aliments dans le nasopharynx ou dans la glotte) ou par parésie des muscles constricteurs sup. et méd. du pharynx (arrêt des aliments dans l'hypopharynx), l'impossibilité complète de déglutition et la présence d'un spasme oesophagien, observés ici, exigent une explication spéciale.

Dans une monographie très détaillée, de 1946, Denise Louis-Bar a rendu compte des divers symptômes du s. d. W., en analysant la littérature et des observations personnelles. Elle s'y occupe aussi des troubles graves de la déglutition, y compris le spasme oesophagien, en citant le travail d'Anderson et coll., selon elle, la seule publication d'un tel spasme. Dans notre note préliminaire, nous nous sommes basé sur l'observation d'Anderson et coll. Une revue approfondie ultérieure de la littérature ancienne et récente nous a montré qu'il existe cependant plusieurs rapports de cas analogues: Reinhold, Wallenberg, van Oordt, Spiller, Antoni, Ramsbottom & Stopford, Merritt & Finland, Benestad,

Spillane, Magnusson, Levine et coll., Stensrud, Hultén-Gyllensten. Dans quelques cas, une alimentation artificielle s'est imposée (comme dans notre cas 1). La dysphagie grave a persisté pendant des semaines, parfois des mois.

Un spasme véritable, ne permettant même pas l'introduction d'une sonde, a été constaté dans les cas de Stensrud et de Benestad; dans le cas de Benestad on a dû pratiquer une gastrostomie (comme dans notre cas 3). Une vérification du spasme par oesophagoscopie et par radiographie fut exécutée dans les cas d'Antoni, d'Anderson et coll., ainsi que dans nos cas 2 et 3¹.

Quelques-uns des auteurs cités essayent d'expliquer le fait singulier qu'une lésion unilatérale du bulbe peut donner lieu à une impossibilité de la déglutition et même à un spasme oesophagien. Antoni a traité le problème à fond. Son point de départ est que la bouche supérieure de l'oesophage, constituée par le muscle crico-pharyngien (muscle de Killian, formant semble-t-il la partie inférieure du muscle constricteur pharyngien inf.), est au repos dans un état de contraction tonique (« Eigentonus »). Il est généralement admis qu'il en est ainsi; Jackson & Jackson mentionnent l'expérience courante faite à l'oesophagoscopie que « ce muscle reste souvent contracturé pendant plusieurs minutes, qui paraissent des heures ». A la déglutition, le muscle s'ouvre « à l'approche du bol alimentaire », par inhibition de son tonus.

Le spasme oesophagien au s. de W. s'explique selon Antoni par un défaut de cette inhibition réfléchrice normale, exercée sur le tonus de repos du muscle crico-pharyngien; ce défaut serait la cause d'une lésion unilatérale du noyau ambigu, notamment de la partie supérieure de celui-ci. Antoni, cependant, attribue aussi un certain rôle au sympathique, indiquant — comme Killian — qu'au niveau du plexus pharyngien, il se mêle au nerf récurrent des fibres sympathiques. Le sympathique aurait alors une influence d'ordre tonique sur le muscle crico-pharyngien. Antoni admet la nature hypothétique de cette explication. Nous reviendrons ultérieurement sur la théorie d'Antoni. Laurell, d'ailleurs, conteste l'explication du spasme, donnée par Antoni, en parlant d'un pseudospasme d'ordre mécanique.

Anderson et col. mettent le noyau dorsal du vague au premier rang, en présumant l'interruption d'un réflexe sensori-moteur, originaire de

¹ Un spasme oesophagien a aussi été constaté au cours de la poliobulbite (Flodgren, Pohl, Sjöberg et coll.). Dans le cas de Flodgren, présentant une parésie unilatérale du pharynx, une sonde ne pouvait pas être introduite. Autrement une lésion bilatérale du vagus peut difficilement être exclue, et selon Knight, Furstenberg et Sjöberg, il est bien établi qu'une telle lésion des deux vagus peut entraîner un spasme de l'oesophage.

la gorge, de sorte que « no inhibition was placed upon the dorsal nucleus to cause its relaxation ». L'arc de réflexe aurait son point de départ dans le faisceau solitaire et irait au noyau dorsal du vague. Ils s'appuient sur Ransom. Selon cet auteur, cependant, l'arc de réflexe cité va aussi au noyau ambigu. Et comme il est généralement admis que le noyau dorsal représente des fonctions autonomes (estomac, intestins, coeur etc.), allant aux muscles lisses, tandis que le noyau ambigu assure l'innervation des muscles striés, y compris le tiers supérieur de l'oesophage, il serait justifié de localiser la lésion au noyau ambigu.

Spillane se rallie à Anderson et coll. en rendant, pourtant, le noyau ambigu responsable; il indique que le foyer au s. de W. pénètre rarement si avant à l'intérieur et à l'arrière qu'il atteint le noyau dorsal. L'expérience tirée de nos observations plaide aussi en faveur d'une lésion du n. ambigu.

Pour expliquer le spasme oesophagien d'origine bulbaire, van Oordt présume une lésion du n. ambigu, supprimant le réflexe du côté homolatéral et du centre coordinateur du côté opposé.

Quelques auteurs supposent une lésion bilatérale du bulbe. Il a été mentionné précédemment qu'une lésion bilatérale du vague entraîne un spasme oesophagien; cela a surtout été démontré par des essais sur les animaux (Knight, Sjöberg). Dans les cas, dont il s'agit ici, rien n'indique une lésion des deux côtés du bulbe.

Enfin il faut noter que Marburg (1911) cherche la cause du spasme dans un effet irritatif par une lésion des racines motrices. Et que Wallenberg (1911) attire l'attention sur la démonstration par Blumenau et Kohnstamm des racines croisées, originaires du n. ambigu.

Pour arriver à une conception claire au regard des théories citées, il faut avouer tout d'abord qu'aucune d'elles n'explique complètement l'origine du spasme oesophagien.

Il existe, ainsi que nous l'avons dit, des discordances sur l'innervation normale de la gorge et de l'oesophage, sur la part qu'ont le n. ambigu et le n. dorsal dans la déglutition normale, sur la représentation relative dans le n. ambigu de l'innervation de la gorge et du larynx (bien qu'il soit généralement admis à présent, que le larynx est représenté en bas, la gorge en haut), et, ajoutons, sur le rôle joué par le sympathique.

Il est pourtant permis d'affirmer quelques faits. C'est par le n. ambigu que le tonus de repos du muscle crico-pharyngien est maintenu. L'impulsion, par laquelle s'exerce à la déglutition l'inhibition réflexe

de ce tonus, aurait son point de départ au niveau du faisceau solitaire. Reste à délibérer si la partie afférente de l'arc de réflexe est d'ordre sensoriel (goût), sensitif (sensibilité au pharynx et à l'hypopharynx) ou bien si elle ne serait pas d'ordre proprioceptif (muscles de la gorge, notamment le muscle constricteur medius), en tant que des troubles du goût et de la sensibilité à la gorge ne sont pas de règle, et qu'ils font défaut même dans les cas aux troubles les plus accusés. Cette dernière possibilité n'a pas été mentionnée par les auteurs cités.

Il nous semble que l'interruption d'un tel arc de réflexe peut donner l'explication de la dysphagie grave, d'origine bulbaire. Mais le spasme, observé parfois, et qui peut persister pendant des mois, s'explique-t-il aussi par une telle interruption de l'arc de réflexe?

Ici on doit peut-être envisager le rôle du sympathique, comme l'ont fait quelques auteurs cités.

Il est généralement admis que le sympathique n'entre pas dans l'innervation de la bouche supérieure de l'oesophage (Louis-Bar). Anderson et coll., eux aussi, avouent que rien n'est noté dans la littérature. Antoni, cependant, suppose que le sympathique augmente le spasme du muscle crico-pharyngien, produit par l'interruption de l'inhibition du tonus de repos de ce muscle. Selon lui, il s'agit d'une prépondérance relative des fibres sympathiques au niveau de la gorge, celles-ci étant mêlées au nerf récurrent dans le plexus pharyngien. Il ne cite pas l'éventualité d'une lésion (d'ordre irritatif?) des voies sympathiques dans le bulbe.

Plus tard, Knight s'est occupé du problème. Par des essais sur les animaux, il a constaté qu'une section unilatérale du vague n'entraîne pas la dysphagie, tandis qu'une section bilatérale produit un spasme de l'oesophage. Le spasme est, selon lui, favorisé par le sympathique.

A la suite d'essais analogues et d'expériences pharmacodynamiques, ainsi que d'observations de poliobulbites, Sjöberg est arrivé à la conviction que le sympathique a « une influence tonisante » sur le muscle crico-pharyngien, ce qui produirait une contracture.

Ainsi, la théorie d'Antoni aurait un support physiologique. Cependant, il est difficile de reporter ces expériences sur les animaux à l'état morbide chez l'homme.

Au lieu de supposer une prépondérance périphérique du sympathique, il serait tenté, pour expliquer les spasmes oesophagiens d'origine bulbaire, d'envisager l'éventualité d'une lésion centrale des fibres sympathiques, au niveau du bulbe. On sait qu'il passe dans la substance réticulée, entre la racine descendante du trijumeau et le n. ambigu, des voies sympathiques efférentes, telles que les voies oculo-pupillaires, vasomotrices, sudorales etc. Dans une note antérieure (1932, p. 752),

nous nous sommes occupés de la représentation relative dans la substance réticulée de ces voies. On peut s'imaginer qu'il passe, près du n. ambigu, des fibres sympathiques efférentes, allant au tractus digestif, ayant un trajet analogue aux fibres oculo-pupillaires: en bas dans la moëlle cervicale, par les rameaux communicants au grand sympathique et aux plexus pharyngien et oesophagien, où les fibres sympathiques se mêleraient aux ramifications du vagus (n. récurrent) (voir Scheller). La lésion d'une telle voie sympathique, qui ne nécessite pas un foyer très profond, ajouterait à la dysphagie, produite par la lésion du n. ambigu et par l'interruption de l'arc de réflexe cité, un élément supplémentaire, susceptible de provoquer, par double effet un réel spasme de l'oesophage.

Ici il faut tenir compte du fait que la lésion de quelques voies sympathiques, situées dans la substance réticulée du bulbe, peut provoquer des troubles paradoxaux, difficilement déchiffrables, de caractère irritatif et lésionnel allant de pair. Nous pensons aux troubles vasomoteurs, sudoraux etc. des syndromes hémibulbaires, ainsi qu'aux douleurs et paresthésies qui peuvent exister au niveau de l'hémiface et de l'hémicorps opposé, dans le domaine d'une analgésie, qui, selon Pette, Foerster ... seraient dues à une lésion simultanée des voies sympathiques. Nous en avons donné une analyse antérieurement (1937). Il y a en somme, lié au syndrome de Wallenberg, tant de phénomènes curieux qu'il faut se rallier à Sjöqvist, l'initiateur de la tractotomie: « this syndrome is one of the most striking that is met with in clinical neurology ».

A titre d'hypothèse, nous présumerons que la dysphagie grave, observée parfois dans le s. de W. relève d'une lésion de la partie frontale du n. ambigu et des voies proprioceptives allant du faisceau solitaire à celui-ci, en supprimant le réflexe ouvrant la bouche supérieure de l'oesophage. Il convient aussi de se demander si le spasme persistant de la bouche (m. crico-pharyngien), observé rarement, ne dépendrait pas d'une lésion simultanée (d'ordre irritatif?) des voies sympathiques dans la substance réticulée.

R É S U M É

Dans le syndrome de Wallenberg, la dysphagie est un phénomène fréquent causé généralement par une parésie du voile du palais et des muscles du pharynx. On observe rarement une impossibilité complète d'avaler, allant dans des cas isolés jusqu'au spasme de la bouche supérieure de l'oesophage. A l'occasion de trois cas, dont il a été rendu

compte, dans l'un desquels il a fallu pratiquer une gastrostomie, nous avons passé en revue les diverses théories invoquées pour l'explication de ce phénomène curieux, et nous émettons une hypothèse impliquant 1) l'interruption par la lésion bulbaire d'un arc de réflexe, portant des fibres proprioceptives du faisceau solitaire au noyau ambigu, et 2) éventuellement la lésion coexistante (d'ordre irritatif?) des voies sympathiques au niveau de la substance réticulée du bulbe.

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HEREDITARY PROXIMAL SPINAL MUSCULAR ATROPHY—A CLINICAL ENTITY SIMULATING PROGRESSIVE MUSCULAR DYSTROPHY

By

GUNNAR WOHLFART, JÖRGEN FEX and
SVEN ELIASSON

INTRODUCTION

Diagnostic muscle biopsies and electromyography have made it possible to classify muscular atrophies accurately without autoptic examination.

Several authors have noticed that cases resembling progressive muscular dystrophy sometimes show fascicular twitchings. Adding two new observations of this type, *Wohlfart* (1942) summarized the pertinent literature in this field. Muscle biopsies in these two cases showed changes, which were interpreted as a combination of dystrophic and neurogenic changes.

Using electromyography *Kugelberg & Welander* (1952) re-examined one of *Wohlfart*'s patients and found neurogenic changes. They collected several cases of similar type and concluded that these cases must constitute a separate hereditary disease.

Welander (1954) mentioned that *Kugelberg & Welander* had also examined a case histopathologically. The examination showed spinal changes localized to the ventral horn.

Scheiffarth (1954) reported three further cases under the name of "Muscular dystrophy with fibrillar twitchings".

It appears that cases of this type are by no means rare and must constitute a separate entity. Three new families are reported in this paper. The differential diagnosis against progressive muscular dystrophy and the Werdnig-Hoffman type of infantile spinal muscular atrophy are discussed.

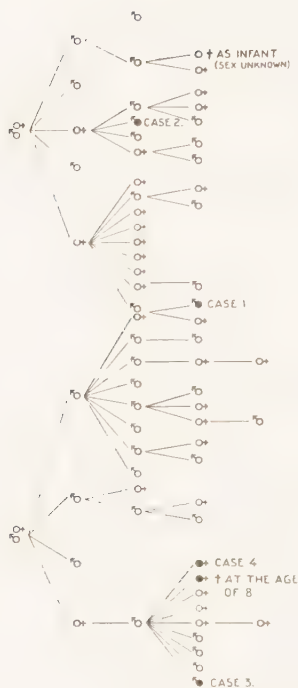


Fig. 1.
Family I.

PERSONAL OBSERVATIONS

Family I.

As is apparent from Fig. 1, this family includes five cases of progressive muscular atrophy. Three of them were examined by us. In one of the other two cases, data were obtained from the records from another hospital.

Case 1.—R. R., male, 23 years. Clerk. Kj 165/51. Pj 3057/54.

He learned to walk at a normal age. At 2 years, however, the parents noted that he often fell down, and at 3 years it was obvious that he suffered from weakness of the muscles. At school he managed fairly well, he could walk and run about, although slowly. At 15 years he was still able to cycle.

From 14 years of age on, the condition became distinctly worse. He found it increasingly difficult to get up from a chair or from a bed. The muscles of the hands and arms have also become weaker but he is still able to do light office work.

Examination: Marked atrophy of the muscles of the shoulders and upper arms, slight atrophy of the muscles of the lower arms and hands. The scapulae were slightly winged. The thigh muscles were markedly atrophic, while the muscles of the lower legs were normal. The facial and sternomastoid muscles were normal. There were continuous but moderate fasciculations generally in the muscles of the trunk and proximal parts of the extremities. He had slight pes equinus bilaterally. Full upward extension of the right arm but not of the left arm. He was unable to get up from a chair and when lying on his back he was unable to lift

his legs from the bed. He walked with a typical waddle. On erection from forward inclination he supported his hands on the thighs or on any suitable object within reach.

The triceps and quadriceps reflexes were very weak, those of the biceps and brachioradialis were slightly weakened, the reflexes of the calves were normal. There was no extensor plantar response. No sensory disturbances were noted.

Mentally he was intelligent but readily depressed.

Electromyography: Single denervation potentials as well as a reduced number of action potentials were recorded in the left quadriceps. Persistent potentials were polyphasic and very large (Fig. 2 a).

Similar findings were made for the left brachioradialis. Widespread synchronization in the quadriceps.

Case 2.—A. S., male, 26 years. Joiner. Kj 189/51.

Development during childhood was normal. Since the age of 14 he had noticed increasing muscular weakness, which had, however, not advanced during the last few years.

Examination: Marked atrophy and paresis of the quadriceps, triceps brachii and deltoideus bilaterally. Moderate atrophy and paresis of the biceps brachii and pectoralis major on both sides. Fairly many fasciculations within these groups of muscles. The facial musculature, sternomastoids, the muscles of the back and the distal muscles of the extremities were normal (Fig. 3).

The quadriceps and triceps reflexes were markedly weakened, the other muscle reflexes were normal. No extensor plantar response. Sensibility: normal.

Considerable creatinuria of 1.05, 1.16 and 1.38 gm as determined on three 24-hour specimens.

Basal metabolic rate: minus 7 per cent.

Cerebrospinal fluid: normal.

Electromyography (quadriceps and triceps brachii): Neurogenic pattern with reduced number of action potentials. A few single denervation potentials (*Feinstein*).

Case 3.—K. N., male, born in 1922, died in 1932. V.F.A. Hälsingborg 173/1924.

He was born at term. He was healthy during the first 3 months of life, after which he had severe whooping cough. Since that time the legs had been flabby and stiff. At 1 year 9 months he was admitted to the Orthopedic Department, Hälsingborg, where severe flaccid paralysis of both legs with commencing pes equinus was noted. During the following years the patient crept around on the floor with the help of his arms and occasionally tried to stand up. He spent the last three years of life in bed. He is said to have been intelligent. Vision was good. He had never been able to control urination or defecation.

Case 4.—M. N., female, 25 years (examined at home).

She had always had weak muscles. She could walk until she was 10 years old, but not since. During the following years there was increasing muscular weakness, which had, however, not advanced during the last few years. No bladder trouble.

Examination: Marked left-convex thoracic scoliosis. General weakness and atrophy of the muscles of the trunk and extremities, particularly in the proximal groups. The muscles of the hand and lower arms were weak, but the patient was able to do light work, such as needlework etc. She was also able to move her toes.

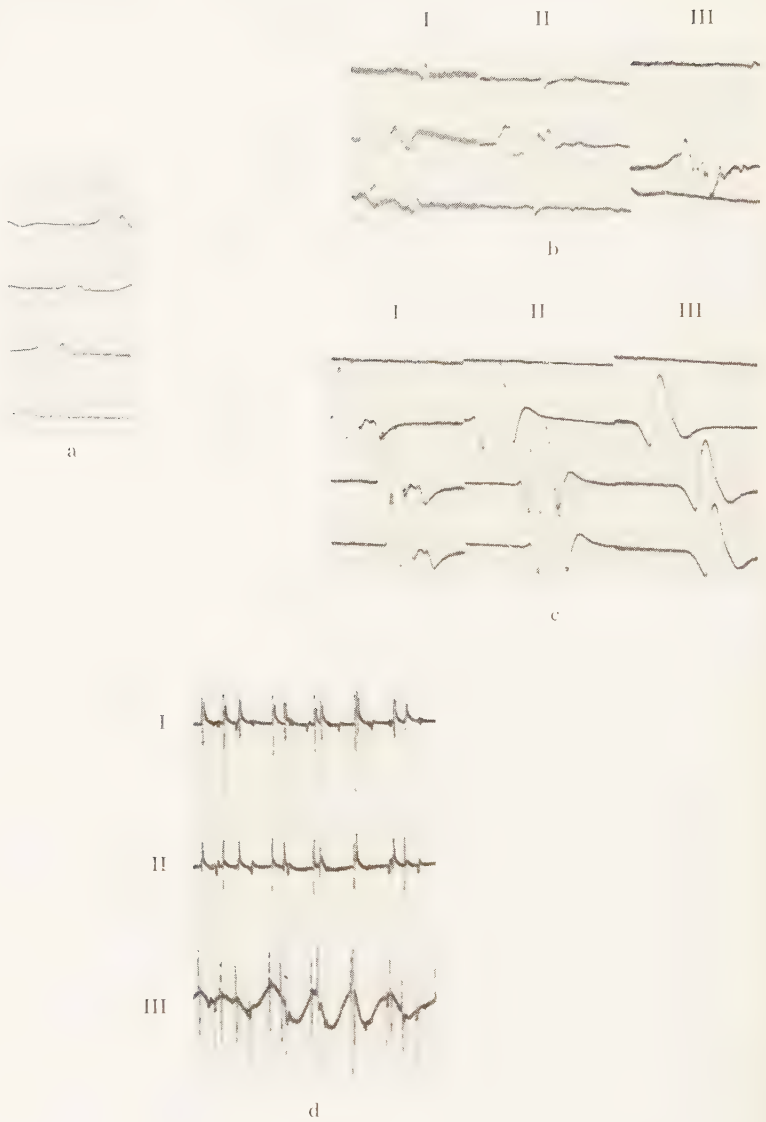


Fig. 2.

Electromyograms.

- a. Case 1, Vastus medialis. Calibr. $750 \mu\text{V}/1 \text{ mm}$, $1.5 \text{ msec} = 1 \text{ mm}$. Giant potentials.
 b. Case 5, Gastrocnemius, medial head. 11, 22 and $22 \mu\text{V}/\text{mm}$, respectively. $1.5 \text{ msec} = 1 \text{ mm}$.

The low potentials in leads I and II are denervation potentials. Polyphasic, synchronous action potentials are seen in all three leads.

- c. Case 5, Tibialis anterior. Calibr. $30 \mu\text{V}/\text{mm}$, $1.5 \text{ msec} = 1 \text{ mm}$. Synchronous, long duration potentials.
 d. Case 5, Tibialis anterior. Calibr. $75 \mu\text{V}/\text{mm}$, $30 \text{ msec} = 1 \text{ mm}$. Synchronization.

Dorsiflexion in the footjoints was impossible. Moderate flexion contracture of both hips. Blue-red discoloration of the feet and lower legs. No pseudohypertrophy. No definite fascicular twitchings.

The brachioradialis reflexes and finger flexor reflexes were elicited, though weakly. No other muscle reflexes could be obtained. No extensor plantar response. No sensory disturbance.

Family II.

Case 5.—B. A., male, 18 years. Kj 104/54.

His parents were healthy. An older brother (32 years old) is healthy. This brother has a 4-year-old son, who at the age of 6 months was admitted to a pediatric clinic and treated under the diagnosis of Werdnig-Hoffman's disease, but later the child made a remarkably good recovery (case 6). Apart from this child, no other members of the family had been known to have nervous or mental diseases.

In early childhood nothing abnormal had been noticed regarding the movements of the patient. When he was learning to walk, however, his muscles appeared weak. It was difficult for him to stand and walk and keep his balance. He always found it difficult to mount steps and to run. His condition gradually became worse, especially during the last few years. During childhood he was able to raise himself from a forwardly bent posture by supporting his hands against his knees, but now he cannot do so. During school age he was driven to school in a car because of difficulty in walking. All the physicians who had been consulted, among others a well-known neurologist, had conceived the case as progressive muscular dystrophy. As a child the patient had often had troublesome respiratory tract infections.

Examination: The patient was in a good general condition. He was fairly obese. The intelligence was good. Examination of the inner organs revealed nothing of interest.

On inspection, no definite signs of muscular atrophy were seen, nor of pseudohypertrophy. No definite fasciculations. The distribution of the pareses closely resembled muscular dystrophy with general weakness of the muscles of the trunk and the proximal muscles of the extremities. The gross functional strength of the hands as well as of the lower arms, was somewhat decreased, but the strength of the lower legs and feet was practically normal. He could not raise himself from a bending posture. After bending he was able to get up if he supported himself against a table or the like. He walked with a marked waddle. The muscle reflexes were generally weakened, except the calf reflexes, which were normal. No sensory disturbances.

Moderate creatinuria: 488, 545 and 585 mg/day, respectively.

Electromyography:

a. *Gastrocnemius:* On insertion and at rest, numerous denervation potentials were seen (Fig. 2 b). Most of the action potentials showed long duration and some of them were markedly polyphasic (Fig. 2 b). There was widespread synchronization (Figs. 2 c and d).

b. *Tibialis anterior:* The action potentials were prolonged and of large amplitude. They showed synchronization but there were no denervation potentials.

Muscle biopsy (tibialis anterior dx): Marked disseminated neurogenic atrophy with groups of normal sized muscle fibers and groups of muscle fibers in various stages of atrophy (Figs. 4 a and b). Some of the normal sized muscle fibers

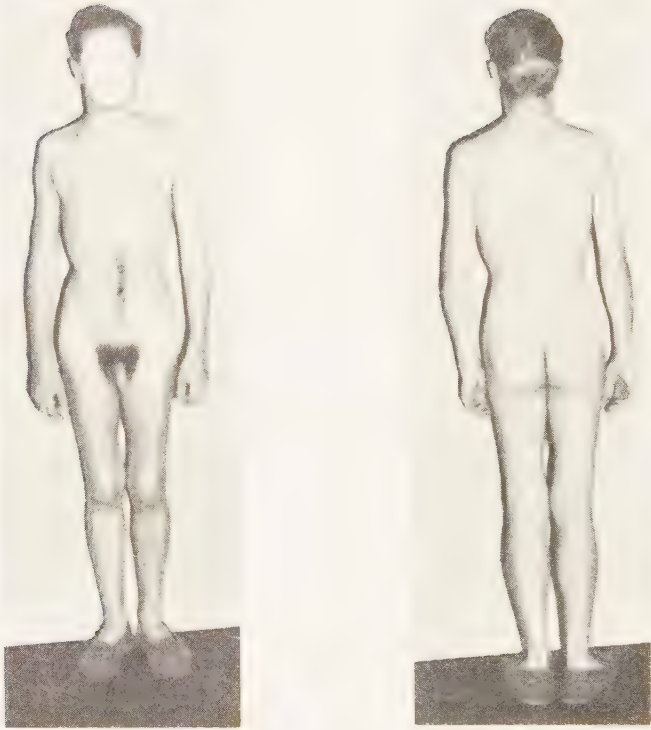


Fig. 3.

Case 2 at the age of 26.

showed a slight immigration of hypolemal nuclei disposed in longitudinal rows. Isolated fibers were in a state of waxy degeneration.

Considerable interstitial connective tissue increase with moderate fat infiltration. Muscle spindles were of normal appearance. One small intramuscular nerve trunk showed a considerable reduction of coarse nerve fibers. No interstitial cellular infiltration.

Case 6.—B. A., 4 years. (Private patient Prof. W.).

Nephew of the patient, case 5. Parents healthy. The patient was born at term, weight at birth 3650 gm. Already during the first months of life it was noted that the patient did not move his legs as much as other children. At 6 months he was admitted to a pediatric clinic and treated under the diagnosis of Werdnig-Hoffmann's disease. The prognosis was regarded as extremely poor. The following notes had been made in the hospital records at that time: "Considerable hypotonia, flabby muscles. He cannot hold the head upright when lying on the back but can lift it when lying in the prone position."

The records contain no notes about the reflexes.

He improved rapidly during the first few months after he had left hospital and at 14 months he was able to walk. His movements were then practically normal. On examination of the patient at 4 years of age, he was found to be of normal

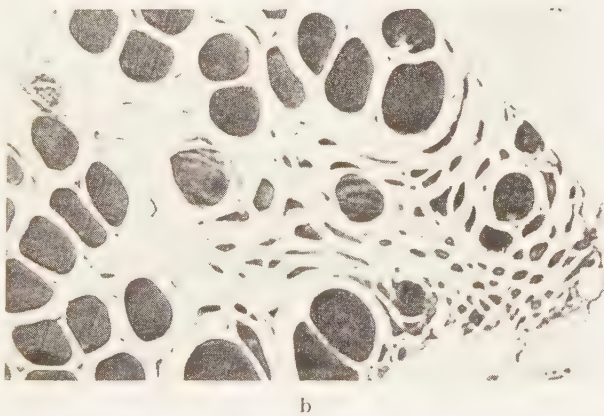
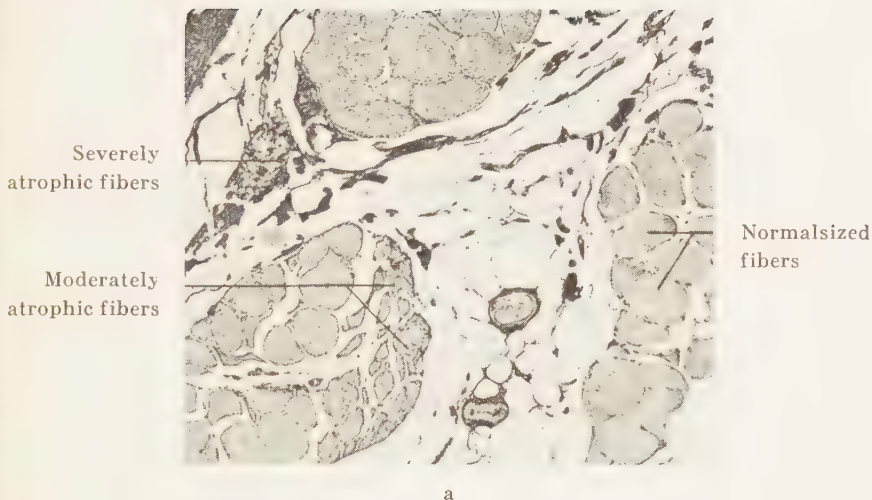


Fig. 4.

Case 5. Biopsy from the anterior tibial muscle.

- a. Hansen's iron hematoxylin-picric acid stain. 80 $\times$. "Successive disseminated neurogenic atrophy".
- b. Osmic impregnation. 100 $\times$. Neurogenic picture. A group of atrophic fibers is seen in a corner of a bundle of normal-sized fibers.

intelligence and could walk and run. However, movements of the legs were clumsy. The only other sign of a pathologic condition was marked flat-footedness bilaterally and absence of the left biceps reflex.

No fasciculations, no pseudohypertrophy.

Family III.

Case 7.—R. E., male, 26 years. Business man. Pj 2965/54.

The father had died young from tuberculosis, the mother was still living and

healthy. A 17-year old sister had weakness of the muscles of the legs for a couple of years. Two stepbrothers were healthy.

As a boy he had been healthy. He had even taken part in sporting competitions (long jump). Since the age of 17-18 years he had noticed increasing weakness of the legs and to a certain extent of the arms, as well as lively twitches in some groups of muscles.

Examination: The quadriceps, brachial biceps and triceps and the major pectoral muscles were moderately wasted and weak. Fascicular twitchings in all of these muscles. Bilateral, moderate ptosis. No other symptoms from the facial muscles. All the other muscles seemed to be strong, except the muscles of the hips, which appeared moderately weak. His gait appeared to be normal. He was not able to raise himself from a squatting posture. He also found it difficult to get up from a chair. The biceps, triceps and quadriceps reflexes could not be elicited. Brachioradialis reflexes were weak bilaterally. The calf reflex was normal. No extensor plantar response. No disturbance of sensibility.

Electromyography (quadriceps and pectoralis major): In both muscles the number of action potentials was reduced. In the quadriceps there were a few single denervation potentials, probably also isolated fasciculations, as well as synchronization. The action potentials were abnormally large. The recording from the pectoralis major showed several complex potential formations with up to 50 msec duration and a number of potentials with an amplitude of more than 2.5 millivolts. There were no denervation potentials and no definite synchronization in the last-named muscle.

Moderate creatinuria: 77, 378 and 480 mg/day, respectively.

COMMENTS

By use of clinical electromyography it is often possible to state with certainty that a given muscular atrophy is of neurogenic origin. The one unequivocal sign is the findings of denervation potentials. The occurrence of prolonged mean duration of action potentials, of increased mean amplitude, of widespread synchronization or of reduced activity as observed on the screen may be of importance, or even conclusive, for the diagnosis.

According to *Buchthal* and co-workers (1943-1953) a pathologic synchronization of the action potentials in a neurogenic atrophy means that it is probably the question of a spinal process.

The electromyogram is also informative in the investigation of primary muscular diseases (*Kugelberg* 1947, *Pinelli* and *Buchthal* 1953, *Wohlfart*, *Feinstein* & *Fex* 1954). The electromyographic findings with progressive muscular dystrophy are still open to debate but it appears that the occurrence of action potentials of extremely short duration or "interference" of the action potentials on weak contraction can support the diagnosis myopathy.

A muscle biopsy can often establish a diagnosis of neurogenic atrophy. Such an atrophy is characterized microscopically by the fact

that the atrophic muscle fibers appear in typical groups in roughly the same stage of atrophy. Furthermore, the number of large nerve fibers in the intramuscular nerve trunks is strikingly reduced.

The initial microscopic changes in muscular dystrophy are not specific. Similar changes occur in other diseases. Not until the dystrophic changes are pronounced, does the microscopic picture become characteristic.

Among the seven cases described, Nos. 1, 2, 5 and 7 were studied electromyographically. All of the patients showed neurogenic changes. Widespread synchronization was seen in three (Nos. 1, 5 and 7), where the potentials were led off by more than 1 electrode. A muscle biopsy specimen was examined from the patient case 5 and showed marked neurogenic changes.

Clinically, cases 1, 2 and 7 closely resembled the cases described in 1942 by *Wohlfart*. In all of these cases there was a proximal form of progressive muscular atrophy with muscle twitchings. The quadriceps and triceps brachii were involved most by the disease.

Case 5 closely resembled the picture of muscle dystrophy and, as a matter of fact, it was not possible clinically to distinguish it from this disease. No fasciculations were observed. In case 4 the picture was also of this type.

Data available about the patient case 3, who was not examined by us, were fairly scanty. This case was included because it occurred in a family with 3 cases examined by us. Finally, case 6 is of interest, because a diagnosis of Werdnig-Hoffmann's disease had later been followed by a strikingly good recovery at 6 months.

The electromyographic and histologic findings in the cases examined in this way thus clearly showed that it was not a question of progressive muscular dystrophy. The electromyographic changes suggest that the atrophy was mainly of neurogenic and probably of spinal nature.

In the cases described by *Wohlfart* in 1942, slight dystrophy-like changes were seen microscopically. Very slight changes of similar type were seen in case 5 in this study. The significance of these changes is not clear. They may be secondary to the neurogenic changes, but not until after autopsy of similar cases can anything be said with certainty. For the time being it is not possible to exclude the possibility of a combination of neurogenic changes and primary myopathy.

At present nothing is known of the reason why atrophy in progressive muscular dystrophy shows a predilection for the proximal groups of muscles. *Kure's theory* (1931) that the proximal muscle groups are supplied by a greater number of sympathetic nerves than

the distal ones and that the disease is due to an affection of sympathetic nerve fibers has generally been abandoned. One has to accept the fact that just as both proximal and distal forms of myopathy occur, hereditary neurogenic muscular atrophy can occur both as a distal (Charcot-Marie-Tooth's disease) and a proximal variant.

Finally it should be considered to what extent the category of cases described might be related to Werdnig-Hoffmann's infantile spinal muscular atrophy or with amyotonia congenita (*Oppenheim*).

The Werdnig-Hoffmann type of hereditary, progressive, infantile spinal muscular atrophy is generally regarded as a distinct entity. Much confusion has, however, arisen from the concept of a special, more benign disease, amyotonia congenita (*Oppenheim*). Many cases of Werdnig-Hoffmann's disease have been reported under the name of amyotonia congenita *Oppenheim*.

Krabbe (1920, 1947) pointed out that cases, which have been described as amyotonia congenita represent really two different diseases, namely (1) a benign disease, which consists of congenital hypotonia, hyperflexibility and weakness, but no wasting. This disease is not familial and can possibly be considered as a retarded development of the muscles. (2) cases which should be regarded as identical with Werdnig-Hoffmann's disease, though they are congenital.

In an extensive monograph *Brandt* (1950) summarized the earlier literature about Werdnig-Hoffmann's and *Oppenheim*'s diseases and concluded on good reasons that "it has not been possible . . . to confirm the existence of any well-characterized disease corresponding to the "Amyotonia congenita" described by *Oppenheim* in 1900. Most of the cases thus designated have been infantile progressive muscular atrophy". *Brandt* also pointed out that "muscular flabbiness" is a fairly common sign in a number of morbid conditions in childhood and expressed the opinion that such cases are sometimes being classified as amyotonia congenita.

Werdnig-Hoffmann's disease has a malignant course. In *Brandt*'s series of 112 cases, 56 per cent died during the first years of life and 80 per cent had died before they were 4 years old. Eight patients reached an age of 15-20 years. The oldest patient was completely disabled at the age of 20.

There are, however, a few reports in the literature indicating a more favourable course in single cases. Thus, *Eger & Ohr* (1942) described a family with two boys, who died during the first months of life with signs of infantile spinal muscular atrophy. Typical changes in the spinal cord were found in one of these cases (the second case was not examined). A sister of these two boys was "völlig schlaff und

bewegungslos" during the first weeks of life, but recovered. At the age of nine she had pronounced lumbar lordosis, but was otherwise normal.

In cases 3 and 6 of the present series the onset dated back to infancy and in the latter case a diagnosis of Werdnig-Hoffmann's disease was made at a pediatric clinic. In case 3 the patient never recovered, but died at 10 years of age. On the other hand in case 6, in which the patient is now only 4 years old, the child has improved considerably. In the other cases in this series the onset occurred during childhood or soon after puberty. The course differed from one case to the other. While in some cases (1, 3, 4, 5 and 7) it was slowly progressive, in cases Nos. 2 and 6 the disease ceased to progress or even regressed.

Paresis and atrophy in Werdnig-Hoffmann's disease is, as in those cases described here, usually first localized to the trunk and proximal parts of the limbs.

We cannot reject the possibility that the category of cases described here might represent a relatively benign variant of Werdnig-Hoffmann's disease, but it appears more likely that it is a question of an independent hereditary disease. At any rate we thought it justified to direct attention to this clinical picture resembling muscular dystrophy, which is obviously of mainly neurogenic nature, as manifested clinically by the frequent occurrence of fasciculations.

SUMMARY

1. Three families with a hereditary type of muscular atrophy clinically resembling muscular dystrophy but of entirely or essentially neurogenic (spinal?) nature are described.
2. The disease is probably genetically independent, but the possibility of its being a relatively benign variant of Werdnig-Hoffmann's hereditary, infantile, spinal, progressive muscular atrophy cannot be excluded.
3. Paresis and atrophy in the category described are localized mainly to the proximal part of the extremities and to the trunk. Fasciculations occur often and similar cases have been described earlier as "muscular dystrophy with fascicular twitchings."

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HEMICRANIE ET HEMIANOPSIE PERMANENTE

(Un cas de migraine symptomatique?)

Par

TORSTEN ØSTERGAARD

Hémianopsie homonyme transitoire est un phénomène qui se retrouve avec assez de fréquence aux accès migraineux. Par contre la littérature décrivant hémianopsie permanente comme complication de migraine nous fournit d'un nombre assez restreint de cas. C'est pourquoi celui qui suit pourrait présenter quelque intérêt en donnant matière à une discussion sur l'importance de ce symptôme et qui porte plus spécialement sur la question s'il s'agit dans des cas semblables d'une migraine symptomatique.

Chez un homme de 49 ans une crise de migraine provoqua une hémianopsie homonyme droite permanente, pour laquelle il fut envoyé à un examen médical. D'après ses informations il y avait eu plusieurs cas d'apoplexie dans la famille de son père; à part de cela aucune disposition familiale aux maladies, surtout aucun cas de migraine. Il fut lui-même auparavant sain d'esprit et de corps. Dans sa jeunesse il avait subi plusieurs traumatismes de la tête, toutes sans perte de connaissance et sans syndrome post-commotionnel. Il nia syphilis de même qu'abus d'alcool, mais fut depuis bien des années grand fumeur – avec une consommation journalière d'environ 20 cigarettes et de deux ou trois pipes de tabac. Depuis l'âge de quinze ans il souffrait d'accès migraineux d'une fréquence alternante – le plus souvent 4 à 5 par an – survenant sans cause extérieure appréciable. Les crises commencèrent par un scotome scintillant dans la moitié droite des champs visuels suivi d'abepsie de la moitié droite, plus tard de maux de tête localisés à la région temporale gauche et à la moitié gauche du derrière de la tête. Très rarement il y eut des nausées aboutissant à des vomissements. Les maux de tête persistèrent une ou deux heures et l'hémianopsie encore deux ou trois heures après la fin de la crise. Tous les deux symptômes avaient pendant la crise la même localisation et la même durée et se perdaient en général au bout de quelques heures, au maximum au bout d'un jour. Durant les intervalles il se sentait bien, sans maux de tête et sans troubles visuels quels que ce soit.

Le matin du 8 avril 1952 il se réveilla avec des maux de tête plus violents que d'habitude, mais de la même localisation qu'autrefois, et accompagnés d'une

ablepsie de la moitié droite du champ visuel. Il n'y eut ni raideur de la nuque, ni nausées ni d'autres gênes. Les maux de tête se perdirent au bout de quelques heures tandis que cette fois-ci l'hémianopsie persista. Un examen neurologique dix jours plus tard ne constata que les troubles visuels et les gênes accompagnants. Le malade ne pouvait plus travailler, en plus il était devenu incapable de se débrouiller seul dans le trafic. Il était devenu craintif et labile d'humeur, ce qu'il n'avait pas été autrefois. Il était bien nourri, avait bonne mine, du genre pychnique légèrement plétorique. Aucun signe d'artériosclérose périphérique. La pression artérielle était 130/90. L'examen neurologique révéla une hémianopsie totale et homonyme du côté droit et pas d'autres anomalies. Le cas étant considéré comme exemple évident d'une migraine symptomatique, il fut admis dans le service neuro-médical à Rigshospitalet, Copenhague. — L'examen ophtalmologique constata de nouveau une hémianopsie homonyme totale du côté droit (avec un évidement étrange de macula en forme d'une chaise), les autres examens furent négatifs. Une carotis-angiographie du côté gauche ne montra pas d'anomalies. Malheureusement, angiographie vertébrale ne fut pas pratiquée. Radiographie du crâne en 5 projections normale. Encéphalographie électrique révéla — par stimulation photographique — une dysrythmie de force moyenne avec des potentiels anomaux à l'arrière. — Il était à supposer qu'il s'agissait d'une petite hémorragie dans les voies visuelles postérieures. Les diagnostics du service furent: Hæmorrhagia intracranialis, obs. pro. Hemianopsia homonyma dextra.

Deux ans se sont passés depuis lors, et j'ai eu l'occasion de le réexaminer récemment. Les troubles visuels sont inchangés, il s'y est habitué et s'est remis à travailler sans grande difficulté. Avec un peu de prudence il se débrouille même dans le trafic et n'est plus craintif. Pendant les derniers deux ans il n'a pas souffert de maux de tête. Cependant, il a changé mentalement: Il est devenu nerveux, se fâche et s'excite vite tandis qu'autrefois il fut d'une nature paisible et équilibrée. Sa femme le trouve même amnésique, chose que le malade lui-même ne veut pas reconnaître. Il a renoncé au tabac et sa consommation d'alcool est extrêmement modeste. Il supporte bien les alcools. — L'examen neurologique montre un état inchangé; à l'exclusion du fait que l'hémianopsie homonyme droite persiste, aucun signe d'affection nerveuse organique. Il y a actuellement des symptômes très nets d'une artériosclérose centrale, les fonds d'œil étant légèrement changés, irrégulièrement calibrés, tordus, aux artères tenues. Le phénomène de Gunn est négatif. Aucun signe d'artériosclérose périphérique, aucun arcus senilis. Pression artérielle 120/70.

La littérature mentionne quelques rares cas semblables: *Thomas* signala en 1907 4 cas de migraine accompagnés d'une hémianopsie homonyme permanente par suite d'un accès migraineux. L'un des malades avait en plus une hémiparèse passagère, les trois autres ne présentaient pas de symptômes accompagnants. Autopsie ne fut pas pratiquée. L'auteur suppose que les accès migraineux ont produit une « softening area of the brain » ce qui aurait eu pour résultat une hémianopsie permanente. *Posey* (1916) et *Wilner* (1921) décrivent chacun leur cas de migraine aboutissant à une hémianopsie homonyme permanente. *Uhthoff* (1927) parmi 127 cas d'hémianopsie homonyme permanente — soit partielle soit totale — en tire 6 qui proviennent d'un scotome scintillant accompagnant une migraine typique d'an-

cienne date. — En 1930 *Adie* signale 6 cas de migraine de longue durée se terminant par une hémianopsie homonyme persistante après un accès. Dans l'un il y avait des symptômes des faisceaux pyramidaux du même côté comme seule anomalie. Ni autopsie ni examens approfondis ne furent pratiqués. L'auteur conçoit les cas comme exemples d'hémorragies subarachnoidales spontanées chez les migraineux, bien qu'il n'y eût qu'un seul cas accompagné de perte de connaissance et de raideur de la nuque. — *Tyson* (1916) et *Daniels* (1932) rapportent chacun un cas d'hémianopsie homonyme transitoire provenant d'une migraine. Dans le dernier l'hémianopsie se perdit au bout d'un mois. Il se trouva que le patient — un homme de 34 ans — souffrait en plus d'une syphilis latente qui fut soignée. L'auteur supposait que l'affection avait son siège en face de corpus geniculatum externum vu l'absence « d'une réaction pupillaire hémianopique ». Voici le cas de *Poos* (1934) : Un homme de 53 ans souffrait entre l'âge de 13 ans et l'âge de 35 ans d'accès migraineux qui s'accompagnaient de scotomes scintillants, de maux de tête, et de diplopie passagère. 18 ans après son dernier accès il fut pris un beau matin d'un vomissement et depuis ce moment persista une hémianopsie homonyme droite qui restait inchangée encore 3 ans plus tard. Il y avait signe d'une artériosclérose (aussi dans les fonds d'œil), la pression artérielle était élevée, et çà et là se trouvaient de légers symptômes neurologiques. D'après *Poos* cette dernière crise équivalait une migraine. Il est pourtant à supposer qu'il s'agit plutôt d'une hémorragie ou d'un thrombose par suite de l'artériosclérose, probablement sans connexion quelle que ce soit avec la migraine antérieure, peut-être dans un foyer (une vaso-anomalie) ayant joué un rôle dans le développement de la migraine. — *Wilson* (1947) ne consacre que très peu de lignes au sujet, à savoir qu'une hémianopsie durant quelques heures jusqu'à deux ou trois jours au delà des crises de migraine se retrouve avec assez de fréquence, mais, lit-on, si une ablepsie partielle persiste, ce qui n'est pas rare, il ne peut pas être question d'une migraine ordinaire. Ensuite *Wilson* mentionne un cas, probablement observé par lui-même : Un homme de 45 ans — « a lifelong martyr of migraine » — avec une hémianopsie homonyme droite persistant depuis une vingtaine d'années qui se trouve de provenir d'une tumeur vasculaire congénitale révélée par une opération. L'auteur ne nous donne pas d'autres renseignements et nous ignorons si l'hémianopsie faisait partie des symptômes accompagnant la migraine du malade. — Je vais maintenant parler d'un ouvrage plus récent — celui de *Donahue* (1950) — qui donne un excellent aperçu de « la migraine et ses manifestations oculaires » se basant sur 206 publications référantes. Un intérêt particulier s'attache ici à la constata-

tion suivante de l'auteur appuyée sur 1600 cas de maladie dans la littérature: des symptômes oculaires d'un genre ou d'autre accompagnent environ 50 % de toutes les crises de migraine et l'hémianopsie est démontrée dans l'aura d'environ 4 % des cas. — Donahue mentionne que les anevrysmes cérébrales peuvent simuler la migraine pendant des longues années. Cela est aussi le cas pour les maux de tête dits histaminiques. Il constate que la plupart des complications de migraine sont dues aux anevrysmes brisées, aux tumeurs non découvertes, ou bien aux thromboses cérébrales vasculaires. Ainsi s'expliquent les rares cas dans lesquels l'hémianopsie ou d'autres transformations oculaires sont devenues permanentes — « migraine per se has never resulted in fatality » —. Cependant, aucune preuve de ces affirmations ne nous est fournie. — Finalement, j'attire l'attention sur une publication intéressante qui vient de paraître: *Mackenzie* (1953) se basant sur 50 cas d'angiomes cérébrales (vérifiées par angiographie) fait le bilan de la symptomatologie, y compris les cas autrefois considérés comme étant du genre migraineux. Il est mentionnée dans l'article que *Olivecrona* (1948) parmi 42 patients souffrant d'une anevrysme artério-veineuse ne trouva qu'une seule céphalée migraineuse. — Dans la documentation de Mackenzie 7 des 50 patients souffraient des maux de tête migraineux. Cependant, certains traits prouvaient toujours à l'examineur attentif qu'il ne se trouvait pas en face d'un cas de migraine typique. Dans les 7 cas les maux de tête étaient toujours localisés au même côté, ils étaient toujours partiels et se trouvaient « on the side of the angioma ». L'auteur dit pour comparer que la migraine typique ne montre que très rarement une localisation constante des maux de tête accompagnants. En plus il fut constaté que les symptômes de l'aura persistent souvent plus ou moins longtemps après la fin de la crise de migraine, ainsi dans deux cas ou les maux de tête furent accompagnés d'une hémianopsie homonyme (passagère). Seulement trois des patients souffrant de maux de tête migraineux revenant périodiquement avaient des dispositions familiales à cette maladie. Donahue conclut « whereas in ordinary migraine the attacks follow a regular pattern in which the aura, lasting usually from a few minutes to half an hour, is then replaced by headache, in these case the aura may be prolonged. It may also persist even after the headache has developed and sometimes the manifestations which one would normally regard as an aura may not develop until after the onset of headache. — All these features indicate that the migraine is in some way atypical. Sometimes abnormal signs are present on physical examination but may be confined to an homonymous defect in the visual field and, although described as occurring in constitutional migraine, must be

suggest the possibility of an angioma being the underlying cause. This is especially likely when the supposed migraine has atypical features to which attention has already been drawn ».

DISCUSSION

Nous avons affaire d'un homme de 49 ans souffrant pendant 33 ans d'accès migraineux. Les maux de tête – toujours du côté gauche – ont été précédés par et accompagnés d'une hémianopsie homonyme droite qui persistait encore deux heures après la fin des maux de tête. La localisation régulière et du même côté de ces symptômes, et le fait que l'aura, l'hémianopsie, persiste durant et après l'accès des maux de tête nous portent à soupçonner d'après *Mackenzie* (1953) la présence d'une migraine symptomatique, plus spécialement d'une angiome cérébrale, vu la longue durée de la maladie. Le fait qu'il n'y eut pas de dispositions familiales à la migraine porte aussi à croire que la migraine décrite n'a pas été typique. Par suite d'une crise à l'âge de 49 ans l'hémianopsie devient permanente. Les deux ans suivants se passent sans crises. – Il est à supposer que cet homme a eu une angiome non vérifiée dans les voies visuelles postérieures, c'est-à-dire un foyer qui d'une part a provoqué les crises migraineuses, d'autre part les a caractérisé de sorte que le tableau devint légèrement atypique comme il a été décrit plus haut. Une carotis-angiographie ne révéla pas l'angiome présumée, probablement parce que la localisation de celle-ci a été une telle que les méthodes d'examen habituelles n'ont pas suffi. Il est possible qu'une angiographie vertébrale eût donné le diagnostic. A un examen de contrôle deux ans plus tard, lorsque l'hémianopsie était devenue permanente et les maux de tête avaient disparu, des signes d'une artériosclérose centrale débutante se révélèrent, et il est à supposer que celle-ci a contribué à l'apparition des symptômes mentionnés – peut-être par une rupture de l'angiome actuellement sclérosée.

Basé sur des études littéraires il faut donc conclure qu'il s'agit dans ce cas-ci d'une hémianopsie symptomatique – bien que les examens n'aient pas révélé le foyer, probablement une angiome placée à l'arrière dans les voies visuelles du côté gauche.

RÉSUMÉ ET CONCLUSION

Un homme de 49 ans – souffrant pendant 33 ans d'accès migraineux et de maux de tête couvrant la moitié gauche du crâne, accompagnés

d'une hémianopsie homonyme droite qui se perd deux heures plus tard que les maux de tête — est pris par suite d'une crise plus violente d'habitude, mais sans complications — d'une hémianopsie homonyme droite qui persiste encore 2 ans plus tard. Aucun accès de céphalée pendant ce temps.

Sur la base d'un examen de littérature et en nous appuyant surtout sur la publication de *Mackenzie* (1953) qui traite la symptomatologie des angiomes cerebrales (50 cas vérifiés), nous concluons qu'il s'agit ici d'une angiome (non-vérifiée) à l'arrière dans les voies visuelles du côté gauche. Cette angiome s'est brisée à cause d'une artériosclérose centrale débutante et a produit une hémianopsie homonyme permanente du côté droit.

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